AMJ
ISSN: 0005-2523

ISSN: 0005-2523
Volume 62, Issue 02, April, 2022

Management of Lipoprotein (a): A Mini Review

Sidhi Laksono[1,2], Pepi Nurapipah[3], Melisa Aziz[4], I Nyoman Wiryawan[5]

Siloam Diagram Heart Hospital, Depok, Indonesia[1]
Faculty of Medicine, University of Muhammadiyah Prof Dr. Hamka, Tangerangm Indonesia[2]
Cililin General Hospital, Bandung Barat, West Java, Indonesia[3]
Faculty of Medicine, University of Pelita Harapan, Tangerang, Indonesia[4]
Department of Cardiology and Vascular Medicine, Faculty of Medicine, University of Udayana, Bali, Indonesia[5]

Coressponidng Author: 1*

Keywords:
Lipoprotein (a), CHD, pharmacogenetic, LDL-C, RNA-i

ABSTRACT

Lipoprotein (a) [Lp[a]] is a particle containing apolipoprotein bind to LDL cholesterol. Lp(a) encoded by LPA gene. Independent from LDL-C level, raised Lpa level by genetic studies shows increasing risk of cardiovascular disease. Prior study shows most of patient with LDL-C controlled by statin still have raised Lp(a) level. Current therapy to lowering LDL-C, could not achieve expected lowered Lp(a) level. Genetic therapy as a novel treatment for lowering Lp(a) is still under investigation. We review several study about Lp(a) correlation with LDL-C, coronary disease, and novel treatment. Most of genetic therapy give promising effect although still under early clinical trial. Prior lipid lowering treatment did not achieve as high as genetic therapy to lowering Lp(a) level.

1. Introduction

Lipoprotein(a) (Lp[a]) is a plasma lipoprotein consisting of a cholesterol-rich LDL particle with one molecule of apolipoprotein B and an additional protein, apolipoprotein(a), attached via a disulfide bond. It is established that plasma Lp(a) levels are primarily genetically determined, with the main determinant being production of apolipoprotein(a) by the LPA gene [1- 5].

Human genetic studies have indicated that plasma Lp(a) is associated with the risk of coronary heart disease (CHD). Apolipoprotein(a), which is encoded by the*LPA* gene, covalently binds to a cholesterol-rich low-density lipoprotein (LDL-C) particle to form Lp(a). Meta-analyses of prospective observational studies by [6] have reported that higher plasma Lp(a) concentration is associated with dose-dependent higher risk of coronary heart disease (CHD) [3], [7].

Gene therapy is a promising therapeutic platform because it targets genes in a sequence-specific manner, which enables more precise and personalized treatment of threatening diseases. RNA-based method offer uniquely targeting the precise nucleic acids involved in a particular disease with greater specificity,

improved potency, and decreased toxicity. This could be particularly powerful for genetic diseases [8].

A genome-wide association study (GWAS) identified variation at the LPA locus to be associated with CHD events [9]. Some studies correlate this process before and after CHD events, other studies correlate how Lp(a) pharmacogenomic affect other lipid profile. This review will discuss how management of Lp(a) with pharmacogenomic process and how this process associated with or without statin therapy influencing CVD risk.

2. Methods

We conducted a literature search on the following databases: PUBMED and Google Scholar. The terms searched for were: Lipoprotein (a), CHD, pharmacogenetic, LDL-C, RNA-I. There was no restriction on the type of studies but there is a language restriction to English and Indonesia only. The inclusion criteria were studies published in the last 10 years. We found 4 article matched with all the keywords on Google scholar, while none with PubMed in the last 10 years. We found 2.711 results on the Lipoprotein(a) keyword, 14.458 on CHD, 12 results on pharmacogenetic lipoprotein(a), 537 results on LDL-C lipoprotein(a), and 1 result on RNA-1 lipoprotein (a). The selection of articles is carried out qualitatively according to the content and the compatibility to the study. The retrieved articles are compiled and maintained using Mendeley software.

3. Discussion

The LPA locus is known for its association with CHD risk and the genetic variants with higher Lp(a) concentrations associated with higher CHD risk. Understanding this process leading to find potentially important drug target for CHD. This finding provides support for exploring strategies to target circulating concentrations of Lp(a) to reduce CHD events [9], [10].

3.1 Association of Lp(a) with lipid profile

Lp(a) particles contain strongly proinflammatory oxidized phospholipids and a unique apoprotein, apo(a), which promotes the growth of an arterial thrombus [2], [4].

Lp(a) is thought to be comprised of an LDL particle and a covalently bound protein product of the LPA gene, apo(a). Study by [10] reveal that even LPA locus has been associated with LDL and total cholesterol in over 100,000 individuals, in this study we found that LPA had nearly twice effect estimation for VLDL associations in same variant. This metabolic link found between circulating Lp(a) with VLDL metabolism is novel.

Study prediction of Lp(a) concentration estimates that Lp(a) concentration appeared to be independent of changes in LDL-C level, this process resembel the relationship of statins, PCSK9 inhibitors, and ezetimibe in CHD risk. in study by [9] shows that Lp(a) levels had an independent association with apparent LDL-c response to statin beyond genotype in these analyses (P = 0.001).(3) The association of the LPA locus with CHD events persisted in individuals with LDL-C ≤70 mg/dL. [2], [4].

Further analysis in CARDS (Collaborative Atorvastatin Diabetes Study) also confirmed that there was no effect of statin on Lp(a) levels, it was only 0.23 mg/dl, (95% CI: 2.25 to 1.80) for difference in Lp(a) levels with atorvastatin versus placebo at one year post-randomization, adjusted for baseline Lp(a), age, and sex [1].

The standard Friedewald formula calculates LDL-c levels that resides in the Lp(a). the result for most

ISSN: 0005-2523
Volume 62, Issue 02, April, 2022

patients there is only about 5% of measurement as LDL-C is estimated to reside in Lp(a), about 8% if the Lp(a) levels are 30–60 mg/dl and as much as 20% if Lp(a) is > 60 mg/dl. The European Atherosclerosis Society proposes the Lp(a) levels should be less than 50 mg/dl for preventative purposes, while The Canadian Cardiovascular Society recommendation is 30 mg/dl [1], [3].

The study results from CARDS trial, statin therapy did not lower Lp(a) levels. The data highlight a more general clinical point that individuals with raised Lp(a) levels for any reason have a lower response to statin therapy. Clinical application from this result that individuals who apparently give lower LDL-C response to statin may be indication for measure Lp(a) levels [1].

3.2 Lp(a) in Cardiovascular Disease

Many studies have found that high Lp(a) to be independent risk factor for atherosclerosis due to its similarity with the plasminogen structure. It can competitively inhibit the conversion of plasminogen to plasmin. It was also found that elevated plasma Lp(a) levels can promote thrombosis [3], [11].

It is increasingly accepted that elevated Lp(a) increases CVD risk, the most common is CHD. GWAS study identified variation of LPA locus to be associated with CHD. Genetic variations at the LPA locus are associated with CHD events during statin therapy is independent from LDL-C lowering. additional events still occurs despite statin therapy in some individuals. This events include individuals after CHD still have the risk of recurrency in high level Lp(a) circulation even with statin therapy. The genetic determinants of this residual cardiovascular risk remain unknown. This finding provides support for exploring strategies to reduce circulating Lp(a) to reduce CHD events in patients receiving statins [1], [7], [9], [11].

Other study by [1] shows although Lp(a) levels are not changed and statin effects on LDL-c appear erroneously low, statin therapy should be continued in individuals with high Lp(a). the reason is statin therapy still have protective effect from CVD in condition with and without elevated Lp(a).

Some reports from Mendelian analysis explain in details why in some level of Lp(a) can provides CHD risk. Despite, this two study from Mendelian analysis explain different study result. Study performed by [6] implied that only persons with very high Lp(a) concentrations are likely to benefit from therapies that reduce Lp(a) concentration. This finding likely explains why therapies that reduce Lp(a) concentration by 20% to 35% have failed providing clear evidence that lowering Lp(a) concentration reduces the risk of CVD events. Eventhough this trial targetting Lp(a) as genetic target.

Study by [12] explain study results by [6] that their estimation of Lp(a)-lowering effect size is overestimated. [12] explain that such Lp(a) with high concentrations have never been observed before in a large white population except for patients with nephrotic syndrome, who have severe disturbances in Lp(a) metabolism, with an overproduction of Lp(a) and other lipoproteins.

These results have important implications for the planning the drugs that target Lp(a) concentrations. While [6] set minimal Lp(a) level should be more than 100 mg/dl to provide clinical effect of Lp(a) therapy, this study pronounced Lp(a)-lowering potential effect is 65.7 mg/dL. Lp(a) level more than 100 mg/dL is overestimate [12].

Instead of the statement, this study by [12] recommended the upcoming first trials should include patients with Lp(a) greater than 100 mg/dL at baseline. By including this type of condition, we can calculate how many doses needed to achieve an Lp(a) concentration less than 30 mg/dL by treatment. To prevent

overestimate of Lp(a) level, the Lp(a) assay used for identification or after treatment have to be well standardized.

Beside raised Lp(a) level with greater risk of CHD, study conducted by xxx reveals that elevated Lp(a) levels may promoting heart failure via an increased risk of CHD and aortic valve disease. Lp(a) levels >90th percentile predict a 2- to 3-fold increased risk of these diseases (14). study conducted by [13] did not shows correlation of Lp(a) concentration and its genetic variants with mortality prognostic in CHD [7].

3.3 Current Genetic Therapeutic

Two common variants in LPA, the gene encoding apolipoprotein(a), rs10455872 and rs3798220 have been found to be associated with CAD risk at odds ratios of 1.70 and of 1.92. Randomized trials of several therapies that reduce Lp(a) levels by 25% to 35% have not provided any evidence that lowering Lp(a) level reduces CHD risk. While emerging therapies using RNA-based approaches effectively lower Lp(a) by as much as 90% by targetting the transcriptional product of the LPA gene [2], [6], [13], [14].

RNA therapeutics refers to the use of oligonucleotides to target primarily RNA.These transcripts include non-coding RNAs such as miRNAs and siRNAs that function in gene regulation. By introducing a specific nucleic acid modality to specific tissue of the patient, gene expression can be downregulated, augmented or corrected [8], [15], [16].

Currently there are two main approaches used to target RNA, there are double stranded RNA-mediated interference (RNAi) and antisense oligonucleotides (ASOs). RNAi operates specifically after transcription process by activating ribonucleases, along with other enzymes and complexes. After the RNA has reach the target, RNA sliced into smaller pieces and undergo degradation process by RNAi and other complex. while Antisense oligonucleotides (ASOs) use different pathway to their target nucleic acid. ASOs bind via Watson Crick base pairing, and inhibit or alter gene expression via steric hindrance, splicing alterations, initiation of target degradation, or other events [15], [16].

SiRNA

RNA interference (RNAi) is a natural defense mechanism for the invasion of exogenous genes. RNAi can knockdown the expression of target genes in a sequence-specifific way. siRNA is RNAi modality which typically can trigger more effificient and specifific gene silencing [15], [16].

siRNA is 7–8 nm in length and 2–3 nm in diameter. siRNAs function by incorporating into a cytoplasmic RNA-induced silencing complex (RISC) to complementary bind target messenger RNA (mRNA) and activate its cleavage. The cleaved mRNA is degraded and thus unavailable for protein translation. [15], [16]

Delivery of siRNAs to the target tissue is a challenge because siRNAs are easily filtered out by the renal system because of its small molecule. SiRNA has to circumvents some barriers before it can achieve gene silencing process. In addition, nucleases in the bloodstream can quickly degrade siRNAs, resulting in a short half-life [9], [15].

There are currently some medicines in trial that selectively target Lp(a):

- AMG 890: AMG 890 is a siRNA designed to reduce the production of Lp(a) by targeting mRNA transcribed from the LPA gene. In this phase 1 study, single-dose treatment in adult with high Lp(a) with AMG 890 doses 9 mg or higher was well-tolerated and significantly reduced Lp(a) with observed maximal percent reductions of > 90% and effects persisting for more than 6 months. in preclinical trial of this drug, Olpasiran (AMG 890) reduced Lp(a) concentrations in transgenic mice and cynomolgus monkeys in a dose-responsive manner, achieving up to over 80% reduction from baseline for 5–8 weeks after administration of a single dose [17], [18].

ISSN: 0005-2523
Volume 62, Issue 02, April, 2022

- SLN 360 is GalNAc-conjugated siRNA targeting *LPA* mRNA in the liver. *In vitro*, the SLN360 sequence potently reduces *LPA* mRNA in primary cynomolgus and human hepatocytes. Specific *LPA* mRNA reduction (up to 91% 2 weeks after dosing) was observed with only the 3mg/kg. In cynomolgus monkeys, >95% Lp(a) reduction at 29 days after 3 doses at 3 mg/kg Q1W; >95% reduction persisted at 7 weeks after third dose [4], [19].

1. SiRNA

Antisense oligonucleotides (ASOs) are short oligonucleotides, single-stranded strings of modifified DNA that are usually 13–20 nucleic acids long and are designed to be complementary to a site on the mRNA target, in this case LPA mRNA. ASOs bind to RNA via Watson-Crick hybridization [2], [15], [16].

ASOs targeting liver since Lp(a) is synthesized in hepatocytes, ASOs targeting LPA mRNA in the hepatocytes to reduce synthesis of apo(a), the most promise in substantially lowering lp(a). ASOs must be able to cross the cell membrane to bind to the target RNA. ASOs are very stable without refrigeration, highly soluble in water, and used in saline solution for their therapeutic potential [2], [5], [15].

There are some under investigation drug to lowering Lp(a) by ASOs:

- Mipomersen: Mipomersen is ASOs that targets apolipoprotein B. ApoB is a core protein in LDL-C. Treatment with Mipomersen decreases ApoB levels without significant deleterious effects on HDL. Even accepted by FDA, Mipomersen failed to achieve European approval [14], [15].
- Pelacarsen is an ASO against apolipoprotein(a) that reduces Lp(a) up to 80% with good tolerability [16].
- Volanesorsen is an ASO against apoC3 that reduces triglyceride levels up to 70% and is being tested in severe hypertriglyceridemic patients. in phase 3 study reveal mean 77% triglyceride reduction by 300 mg once a week, s.c. injection [16], [20].
- Vupanorsen is an ASO against ANGPTL3 that reduced triglyceride levels 36–53% among. moderate hypertriglyceridemic individuals [16].

ASOs delivery by parenteral injection, such as intravenous infusion or subcutaneous injection is the main method of delivery. ASOs transferred from the blood to the tissues in minutes to hours. ASOs can reside for 2-4 weeks before degradation [15].

3.4 Other theupeutic option

Before investigating RNAi-based therapy, there are current drugs used to reduced Lp(a) level.

1. Statin: Substantial heterogeneity between statin drugs in a meta-analysis of RCTs. Effects ranged from 13% reduction (95% CI 10–15%) for atorvastatin in the CARDS study to 15% increase (95% CI 13–17%) for simvastatin in the 4S study [4].
2. PCSK9: PCSK9 inhibitors reduce Lp(a) levels by <15%-30%. PCSK9 inhibitor reduce Lp(a) level if it was >50 mg/dl and not effective if the baseline level of Lp(a) is too high. Median Lp(a) reduction with evolocumab was 26.9% [interquartile range (IQR) 6.2–46.7%) in the FOURIER study. Median reduction with alirocumab was 25.6% (IQR 7.2–42.7%) in pooled phase 3 trial data [2], [4], [5].
3. Niacin: Niacin reduces Lp(a) levels 20–30% by inhibiting the LPA promoter.Reduced by 22.9% (95% CI 18.5–22.9%) in a meta-analysis of RCTs [4], [5].
4. The cholesteryl ester transfer protein (CETP) : CETP inhibitors reduce plasma Lp(a) concentrations by 20%–40%. in phase 2 study, Evacetrapib (CETP) reduced Lp(a) by up to 40%. Either Anacetrapib reduced Lp(a) by 34.1% in a small phase 2 study.
5. Lipoprotein apheresis (LA): LA is a therapeutic option when prior therapy could not lowering both LDL-C and Lp(a).(18) Apheresis has a potent effect in lowering Lp(a) levels. There are several

methods of LA using different physicochemical principles, ie, filtration, precipitation, or adsorption. Elevated baseline levels of Lp(a) were reduced ≈70% immediately after LA sessions. In patient with chronic LA, rebound elevation of Lp(a) is almost 80% from baseline level before next treatment [2], [5], [14].

3.5 Limitation of genotyping

Genotyping process in some platforms could not detect every single nucleotide polymorphisms (SNPs) in the genome, particularly in smaller diameter. Some variants reported by a GWAS are often not the true causal variant at the cognate locus [19], [20].

GWAS genotyping platform generally only detects SNP that found commonly in the population, with typically minor allele frequency (MAF) >5%, despite low frequency variants (MAF<5%) that poorly detected may have larger phenotypic effects [21].

In pharmacologic response, there could be confounding factors influence Lp(a) level after treatment e.g. steroid hormones suppress apolipoprotein(a) synthesis, while growth hormone increases Lp(a) levels, or antithrombotic associations that may alter the result than estimation, here may produce clinically meaningful reductions in CHD risk [5], [6].

In the end, while the variants that have been discovered may not have immediate clinical utility in predicting the occurrence of CHD now, in the later they do have substantial potential to reveal novel pathogenic mechanisms, and to suggest targets for prevention and therapy [21].

4. Conclusion

Lp(a) is plasma protein bind to LDL-C, Lp(a) primarily affected by genetic. Instead of other therapeutic option, genetic therapy is novel primary choice to lowering Lp(a). In the treatment of statin, Lp(a) level is independent with LDL-C level. Lp(a) give significant effect in the pathophysiology of CHD and other CVD event eg valvular heart disease. It is still questioned wheter Lp(a) level has similar effect in after-CHD event patient.

To achieve clinical effect, several drugs and method shows different set point for lowering Lp(a) level which vary from several trial. Current option of genetic therapy to lowering Lp(a) is siRNA and ASOs. Other prior therapeutic option does not reach expected level in lowering Lp(a) as effective as RNAi-based therapy. while genomic therapy is novel and in high feature of research, genotherapy still have many limitation and need for more trial and research to achieve expected clinical effect.

5. References

[1] H. A. Deshmukh et al., “Genome-wide association study of genetic determinants of LDL-c response to atorvastatin therapy: importance of Lp(a).,” J. Lipid Res., vol. 53, no. 5, pp. 1000–1011, May 2012.

[2] A. Vuorio, G. F. Watts, W. J. Schneider, S. Tsimikas, and P. T. Kovanen, “Familial hypercholesterolemia and elevated lipoprotein(a): double heritable risk and new therapeutic opportunities.,” J. Intern. Med., vol. 287, no. 1, pp. 2–18, Jan. 2020.

[3] J.-X. Gu et al., “Lipoprotein(a) levels and genetic polymorphisms in LPA genes may contribute to risk of coronary heart disease,” Int J Clin Exp Med, vol. 12, no. 8, pp. 10845–10850, 2019.

ISSN: 0005-2523
Volume 62, Issue 02, April, 2022

[4] D. I. Swerdlow, D. A. Rider, A. Yavari, M. Wikström Lindholm, G. V Campion, and S. E. Nissen, "Treatment and prevention of lipoprotein(a)-mediated cardiovascular disease: the emerging potential of RNA interference therapeutics," Cardiovasc. Res., vol. 118, no. 5, pp. 1218–1231, Apr. 2022.

[5] S. Tsimikas, P. L. S. M. Gordts, C. Nora, C. Yeang, and J. L. Witztum, "Statin therapy increases lipoprotein(a) levels.," Eur. Heart J., vol. 41, no. 24, pp. 2275–2284, Jun. 2020.

[6] S. Burgess et al., "Association of LPA Variants With Risk of Coronary Disease and the Implications for Lipoprotein(a)-Lowering Therapies: A Mendelian Randomization Analysis.," JAMA Cardiol., vol. 3, no. 7, pp. 619–627, Jul. 2018.

[7] P. R. Kamstrup, "Lipoprotein(a) and Cardiovascular Disease.," Clin. Chem., vol. 67, no. 1, pp. 154–166, Jan. 2021.

[8] B. Hu et al., "Therapeutic siRNA: state of the art.," Signal Transduct. Target. Ther., vol. 5, no. 1, p. 101, Jun. 2020.

[9] W.-Q. Wei et al., "LPA Variants Are Associated With Residual Cardiovascular Risk in Patients Receiving Statins.," Circulation, vol. 138, no. 17, pp. 1839–1849, Oct. 2018.

[10] J. Kettunen et al., "Genome-wide study for circulating metabolites identifies 62 loci and reveals novel systemic effects of LPA.," Nat. Commun., vol. 7, p. 11122, Mar. 2016.

[11] J. Guertin et al., "Sex-Specific Associations of Genetically Predicted Circulating Lp(a) (Lipoprotein(a)) and Hepatic LPA Gene Expression Levels With Cardiovascular Outcomes: Mendelian Randomization and Observational Analyses.," Circ. Genomic Precis. Med., vol. 14, no. 4, p. e003271, Aug. 2021.

[12] C. Lamina and F. Kronenberg, "Estimation of the Required Lipoprotein(a)-Lowering Therapeutic Effect Size for Reduction in Coronary Heart Disease Outcomes: A Mendelian Randomization Analysis.," JAMA Cardiol., vol. 4, no. 6, pp. 575–579, Jun. 2019.

[13] S. Zewinger et al., "Relations between lipoprotein(a) concentrations, LPA genetic variants, and the risk of mortality in patients with established coronary heart disease: a molecular and genetic association study.," lancet. Diabetes Endocrinol., vol. 5, no. 7, pp. 534–543, Jul. 2017.

[14] J. Leebmann et al., "Lipoprotein apheresis in patients with maximally tolerated lipid-lowering therapy, lipoprotein(a)-hyperlipoproteinemia, and progressive cardiovascular disease: prospective observational multicenter study.," Circulation, vol. 128, no. 24, pp. 2567–2576, Dec. 2013.

[15] J. Chery, "RNA therapeutics: RNAi and antisense mechanisms and clinical applications.," Postdoc J. a J. Postdr. Res. Postdr. Aff., vol. 4, no. 7, pp. 35–50, Jul. 2016.

[16] M. H. Miname, V. Z. Rocha, and R. D. Santos, "The Role of RNA-Targeted Therapeutics to Reduce ASCVD Risk: What Have We Learned Recently?," Curr. Atheroscler. Rep., vol. 23, no. 8, p. 40, Jun. 2021.

[17] M. J. Koren et al., “Preclinical development and phase 1 trial of a novel siRNA targeting lipoprotein(a).,” Nat. Med., vol. 28, no. 1, pp. 96–103, Jan. 2022.

[18] M. J. Koren et al., “Safety, Tolerability and Efficacy of Single-dose Amg 890, a Novel Sirna Targeting Lp(a), in Healthy Subjects and Subjects With Elevated Lp(a),” vol. 13, no. 3, p. 2853, 2020.

[19] D. A. Rider et al., “Pre-clinical assessment of SLN360, a novel siRNA targeting LPA, developed to address elevated lipoprotein (a) in cardiovascular disease,” Atherosclerosis, 2022.

[20] A. Tirronen, K. Hokkanen, T. Vuorio, and S. Ylä-Herttuala, “Recent advances in novel therapies for lipid disorders.,” Hum. Mol. Genet., vol. 28, no. R1, pp. R49–R54, Oct. 2019.

[21] D. I. Swerdlow, M. V Holmes, S. Harrison, and S. E. Humphries, “The genetics of coronary heart disease,” Br. Med. Bull., vol. 102, no. 1, pp. 59–77, Jun. 2012.