HEALTHY HEART

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39 year old patient had a cardiac arrest and died. His post mortem was suggestive of severe CAD and lipoprotein(a) (Lp(a)) of 300 mg/dl. He was getting his regular body check-up, which was normal as he had a strong family history of young sudden death. Was extra could have been offered to the patient as preventive strategy ?

62 year old patient had recurrent MI within 2 years with LDL of 70 mg/dl and strong family history. His LDL was reduced to only 30% in spite of Rx with high dose of statin of Ezetimibe (Disproportionate LDL reduction). What could be the reason for the recurrence of cardiac events and lesser than predicted LDL reduction? Lp(a) was done which was 180 mg. What extra can be done to prevent the recurrence of CV events ?

In recent years we have a better understanding of the structure and function of Lp(a) as well as newer guidelines with clear indication of Lp(a) testing and specific therapy for Lp(a), which is very effective. Let's know about Lp(a).

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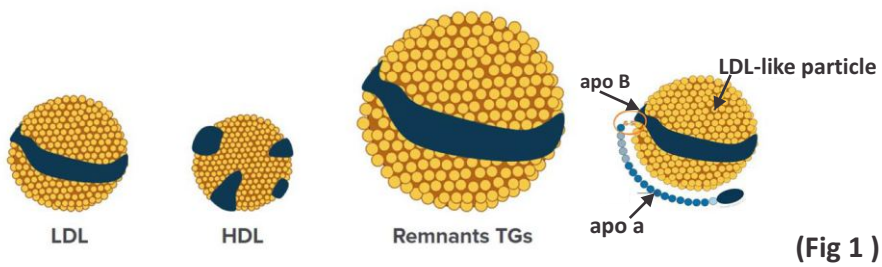
From Genes to Treatment
What All Physician Should Know About Lp(a)?

Clinical Focus on Lipoproteins for CVD Prevention



(Fig 1)

Structure of Lp(a)

Let's first understand the structure and composition of Lp(a). Lp(a) consists of a low density lipoprotein (LDL) particle, containing of course its key protein, apolipoprotein B 100 (apoB 100), together with a second protein, which is exclusively of hypnotic origin, apolipoprotein(a) (apo[a]) which is spread around the surface of the particle and linked by disulfide bond **(Fig 1).**

When we look at the distribution of Lp(a) levels in the general population, roughly 30% of the population have Lp(a) greater than 30 mg/dL and roughly 20% have Lp(a) greater than 50 mg/dL. They are rarely detected since Lp(a) still is rarely measured.

With Increase in Lp(a) concentrations > 30 mg/dL, the risk for myocardial infarction (MI) increases; and more so when the level goes above 50 mg/dL. **(Fig 2)** This is true both patients on statin or without statin **(Fig 3)**. When we compare the CV risk for other lipoprotein classes, for similar increase of LDL or remnant trigly-cerides, the maximum risk is there for LPa **(Fig 4).**

Lpa is not only a risk factor for CAD but

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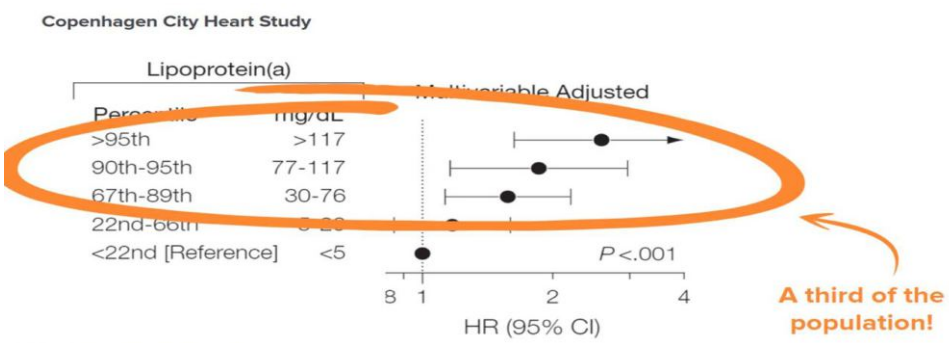
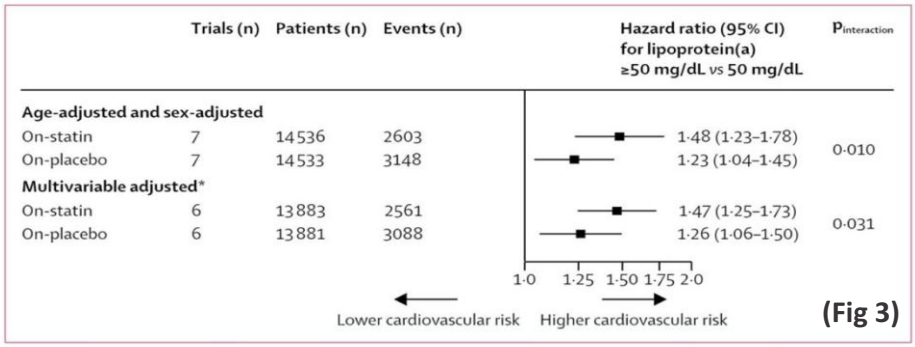
Lp(a) Levels and Risk of MI **(Fig 2)**



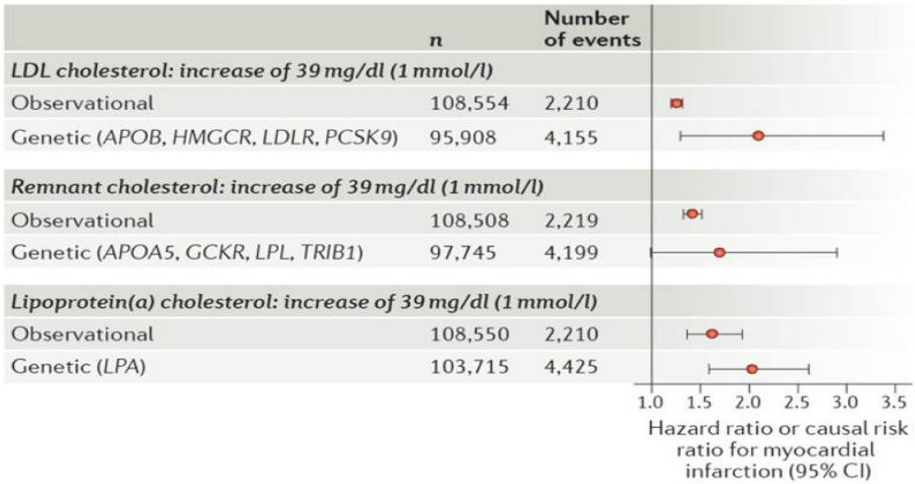
Comparative predictive value of on-statin vs on-placebo Lp(a) concentrations for incident CVD



(Fig 3)

Lipoprotein Classes and Risk of MI

Copenhagen General Population Study **(Fig 4)**



also for aortic stenosis, heart failure, ischemic stroke especially in young adults, PVD or total cardiovascular mortality. **(fig 5)** Most importantly, Mendelian-randomization studies also support that Lp(a) is a causal risk factor for CVD. More than 90% of the Lp(a) concentrations are genetically determined with genes on chromosome 6q26-27. Gene for apo(a) is derived through the course of evolution from the plasminogen gene which increases thrombogenesis.

When we look in families where we can see people with alleles identical So we know now that high Lp(a) is associated with an increased risk for CVD and we also know that genetic variants, like the small apo(a) isoforms or the two SNPs to have a strong association with high Lp(a) concentrations and these variants are also strongly associated with an increased risk for CVD.

How is LPA measured ?

Historically, Lp(a) measurements have been reported in mg/dL; however, recognizing that the mass of Lp(a) particles vary significantly with apo(a) isoform size, and increased risk of CVD is typically seen for high concentrations of small isoforms, nmol/L is now the recommended unit. At present, labs may report levels in either unit dependent on the assay used. It is therefore important to pay attention to the unit used by your lab for reporting. Lp(a) levels remains steady throughout life so serial level are currently not recommended.

Guideline Recommendations

Now slowly but steadily, interest is increasing on antagonizing this risk. In 2019, ESC Guideline and Indian Guideline has actually expanded the indication stating that of Lp(a) testing should once be done in every single patient, who are evaluated with lipid testing for cardiovascular risk.

Just recently published 2021 Canadian Cardiovascular Society Guidelines give a very nice insight on Lp(a). The

first part is Lp(a) testing for cardiovascular risk reclassification as Lpa illustrating the major impact of this particle on risk. Now the second part in the Canadian guidelines conveys to the Lp(a) testing for therapeutic decisions. In both primary and secondary prevention, you will go for an intensification of your LDL-lowering therapy and controlling other risk factor very aggressively if Lp(a) is very high.

So, if we make it simple and look at the key recommendations for Lp(a) testing, it is advised to perform Lp(a) testing in all persons, for initial CV risk assessment and also mandatory if they were so-called LDL cholesterol hypo-responder to statins because we know that statins are less effective in subjects with very high Lp(a) due to of the pollution of the LDL value by Lp(a).

Treatment : One of the problems that we face in patients with elevated Lp(a) is our limited and variable response to current treatments **(Fig 6)**. We certainly do try to improve our life-style, but it has minimal effect. Statins are recommended to lower LDL aggressively. There is some data about estrogen and niacin but it has really not demonstrated benefit in randomized control trials. There is some data for aspirin though not very robust, from The Women's Health Initiative sub study showed that in people with elevated Lp(a), aspirin reduces risk by almost two fold.

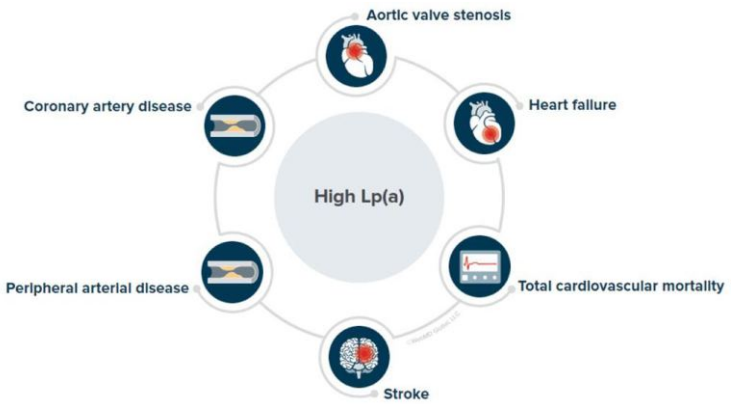
Apheresis was performed and achieved a 66% reduction in Lp(a) and also LDL. The risk for MI, percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG) in 2 years was significantly less after starting apheresis. These were done with retrospective controls and not done randomized controlled parallel group studies. This therapy is also not patient friendly.

With PCSK9 inhibitor-Evolocumab, there was a modest reduction of about 36 nanomoles per liter in the top quartile of reduction in Lp(a) in the FOURIER Trial. In people with Lp(a) less than the median, the HR was 0.85, and in people with Lp(a) greater than the median, the HR was 0.76, suggesting a better benefit in these patients with an elevated Lp(a) **(Fig 7)**.

The real question is whether any specific therapy can be made to reduce Lp(a) as Lp(a) is genetically determined.

The answer to this problem is a technique known as gene silencing, a DNA-based therapy that uses an antisense strand. In this technique a single-stranded DNA light therapy is given. It goes into the hepatocytes and it combines with messenger RNA for apo(a) and then resulting complex is

Lp(a) Levels and Other Outcomes



(Fig 5)

Can Elevated Lp(a) Be Pharmacologically Addressed ?

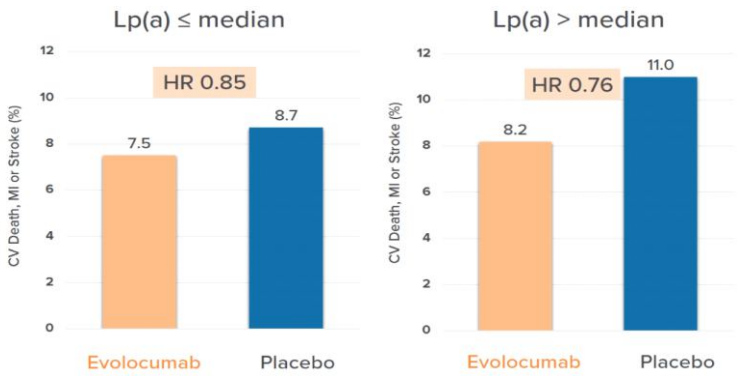
Strategy	Mechanism	Lp(a) Reduction	LDL-C Reduction
Statins	Increased LDLR expression	0%-7%	50%
Niacin	Reduced apo(a) transcription or apo B_{100} secretion	20%	13%
CETP Inhibitor	Inhibition of apo B_{100} lipidation	24%-36%	36%-42%
PCSK9 inhibition	Inhibition of LDLR degradation, decreased apo B_{100} formation	25%	40%-59%
Apheresis	Removal of circulating apo B_{100} lipoproteins	~ 70%	up to 75%
Apo(a) antisense	Decrease hepatic apo(a) synthesis	Up to 78%	No effect

(Fig 6)

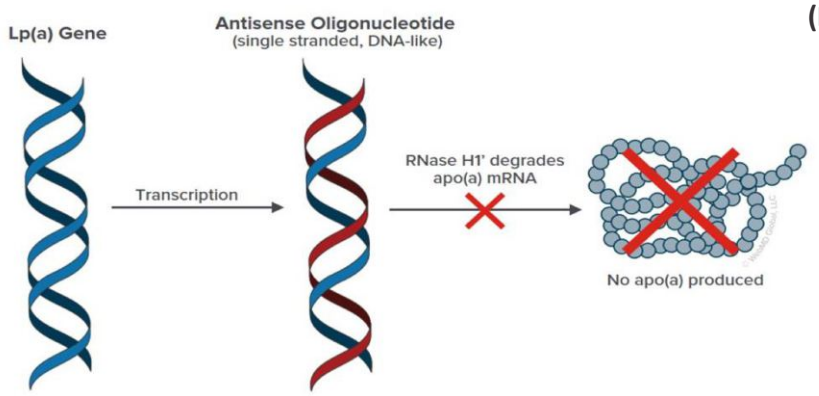
degraded by RNase, so that no apo(a) is produced **(Fig 8)**. A breakthrough in this therapy was the development of GalNAc or N-acetylgala-ctosamine as a way of directing the ASO into the hepatocyte. This results in better delivery to the hepatocyte with roughly a 30-fold increase in the effectiveness, and hence a 30-fold decrease in the dose, which improves safety and tolerability.

Here, you see that there was up to 80% reduction in the level of Lp(a) and that development led to the phase three trial. So, we are now conducting a clinical trial at a thousand sites in approximately 48 countries known as the HORIZON trial. In this trial approximately 8,000 patients with established coronary disease in two strata with levels >70 mg/dL and > 90 mg/dL as add on to optimal background therapies. They were randomized to either GalNAc ASO now known pelacarsen 80 mg given subcutaneously monthly or placebo for four years. The primary endpoint is four component major adverse cardiac events (MACE).

FOURIER Trial : Effect of Evolocumab by Baseline Lp(a) **(Fig 7)**



Lp(a) Antisense Oligonucleotide Therapy **(Fig 8)**



CONCLUSION

Lp(a) simply consists of (an) LDL-like particle with a second protein, apo(a). Importantly, about 30% of possible weight in Lp(a) is in fact cholesterol. The main determinant of Lp(a) is the polymorphism, that is replication or multiplication of the KIV 2 structure in the apo(a) gene. The frequency of elevated Lp(a) levels above and beyond 50 mg/dL in the general population is of the order of one in six. Lp(a) causes and is an independent risk factor for cardiovascular disease, including MI, ischemic stroke and aortic valve stenosis. Lp(a) testing could not only impact the risk stratification for given patient but can equally influence the therapeutic strategy. If we now move on to consider present guideline recommendations in patients with elevated levels of Lp(a), treatment intensification of all risk factors or modifiable risk factors is strongly recommended as no specific therapy is there for LPa reduction at present.

2019 ESC/EAS guideline and Canadian Guideline as well as Indian guideline strongly recommends that a once in a lifetime measurement of Lp(a) is essential.

Interest in LPa is seen recent years is their as specific therapy using an antisense oligonucleotide (ASO) or short interfering RNA (siRNA) is invented as a strategy for lowering Lp(a).

Important cardiovascular outcome trial is actually ongoing using a highly efficacious ASO therapy to be given as once a month s/c injection – HORIZON trial. Marengo CIMS Hospital center is one of the center for this study. Enrollment is over worldwide and results are awaited.

Till the result of this study comes we have very limited options like giving Aspirin, controlling other risk factors very aggressively, and using PCSK 9 inhibitors, especially as secondary prophylaxis in the high-risk subgroup.

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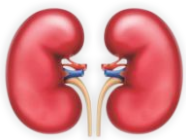
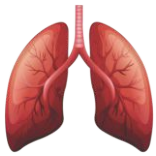
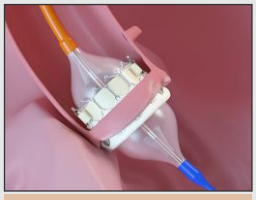


31 Kidney Transplants

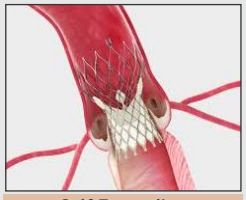
171 Paediatric BMT



Lung Transplant



Balloon Expandable Valve



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