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CARDIOVASCULAR RISK USING SERUM LIPOPROTEIN (A) CONCENTRATION LEVELS IN HIV POSITIVE PATIENTS ON HAART AT LIVINGSTONE GENERAL HOSPITAL, LIVINGSTONE, ZAMBIA.

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Abstract: Purpose: Data on Lipoprotein (a) (Lp (a)) levels and it's accompanied risk for CVD in HIV positive patients on HAART in Zambia being limited, the study was conducted to provide the distribution of Lp (a) and to determine the risk categories for developing CVD using Lp (a) and LDL-c concentration levels in HIV patients on HAART at Livingstone General Hospital. **Methods**: This cross sectional study was conducted between December 2014 and February 2015 at Livingstone General Hospital. Routine serum samples were collected and sent to the University Teaching Hospital Biochemistry laboratory for the determination of Lp (a) & LDL-c concentration levels on Beckman coulter AU480 analyzer. Data was analyzed using STATA v.12 and SPSS v.17. **Results:** Based on their Lp(a) levels, 48% were at low risk; 29% at high risk and 2% at very high risk for CVD. Only 7.7% were at risk for CVD based on their LDL-c level. Age (p=0.009) and duration on HAART (P<0.001) were significantly associated with high Lp (a). **Conclusion:** The percentage of HIV positive patients on HAART who were at risk for developing CVD using Lp (a) concentration levels was high. However, their LDL-c concentrations were fairly distributed with the majority having values within normal reference.

Key words: Lipoprotein (a), Risk category, Highly Active Antiretroviral Therapy, HIV, Cardiovascular Disease.

Introduction

Cardiovascular disease (CVD) is the number one cause of mortality worldwide and over the last few decades, it has become clear that chronic CVDs and risk factors are on the rise on the African continent especially in HIV Positive individuals on HAART[1,2]. A meta-analysis study involving 25 African countries showed that more than one-thirdof HIV-seropositive patients on combined antiretroviral therapy had some form of cardiovascular disorders. They reported a prevalence of 42.3% with Myocardial infarction in India, 30.0% prevalence of CV Autonomic neuropathy in Mozambique, 17.7% prevalence of dilated cardiomyopathy in Rwanda, 37.4% prevalence of QTc interval prolongation in Nigeria. Use of first-line antiretroviral therapy regimens were associated with raised total cholesterol, LDL-cholesterol,

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and triglycerides and they recommended that Lipid profiles should be performed at baseline before commencement of antiretroviral therapy and then periodically through treatment follow-up to monitor any rising trends[3,4,5].

A large body of genetic and epidemiological evidence now suggests a direct association between an elevated plasma lipoprotein (a) (Lp(a)) level and an increased risk of CVD. Lp(a) levels are, to a major extent, regulated by genetics, and thus less affected by nongenetic factors[6].

The plasma concentration of Lp(a) varies over a wide range among individuals. Furthermore, the inter-individual variation in Lp(a) level is 90% genetically determined, although plasma Lp(a) in a particular individual remains stable over a lifetime[7].

However, with the advent of HAART, Lp(a) has been shown to be significantly raised in HIV positive patients receiving treatment and interestingly, high Lp(a) levels seem to be characteristic of all black populations so far studied [8-11]. This may suggest that blacks are more susceptible to CVD than whites in relation to Lp(a) levels in HIV patients on HAART, although this matter warrants further investigation.

In an earlier study on HIV-positive individuals initiating ART with mainly unboosted HIV protease inhibitors (PI), an increase in Lp(a) was observed, in particular in patients with higher Lp(a) baseline levels[12].

Another study showed that those treated with HAART for 12 months had significantly higher levels of Lp(a) in comparison with those treated for six months (p=0.034) [13].

Lp(a) Pathology and CVD relation

Lp(a) may be athero-thrombotic through its low-density lipoprotein moiety, but also through Apo(a). Apo(a) can be retained in the vessel wall and thereby mediate pro-inflammatory and pro-apoptotic effects including those potentiated by oxidized phospholipids. Apo (a) may also exert anti-fibrinolytic effects[13, 14].

Lp(a) belongs to the lipoproteins with the strongest atherogenic effect.Increased risk of atherosclerotic vasculopathiessuch as coronary heart disease, abdominal aneurysm,peripheral vasculopathy, ischemic stroke, peripheral arterial occlusive disease, cerebral strokeassociated with elevated Lp(a) plasma concentrations have been reported and conversely, persons with very low or no detectable Lp(a) plasma concentrations did not present a specific phenotype[15-17].

A meta-analysis of prospective studies demonstrated that elevated levels of Lp(a) was an independent risk factor for CVD and that the pro-atherogenic influence of Lp(a) seemed to be particularly enhanced in subjects with elevated levels of LDL cholesterol (LDL-c)[18-20].

Most studies with the aim of defining an absolute threshold of Lp(a) serum concentration have reported an approximately two fold increase in cardiovascular risk in patients with Lp(a) ≥30 mg/dL compared with patients with Lp(a) levels <30 mg/dL. However, the increase in cardiovascular risk attributable to high Lp(a) is further modulated by other cardiovascular risk factors, in particular LDL-c[21-23].

There was scarce information if any,of studies that had been conducted that particularly reported risk categories for developing cardiovascular disease using Lp(a) concentration levels in HIV positive individuals on HAART, so this study was conducted to provide such information as this. In fact, Lp(a) levels among HIV positive patients treated with HAART in Zambia was unknown, so it was not known, how many in the HIV positive patient population receiving treatment had high levels of Lp(a) and at great risk of developing CVD especially those with longer duration on HAART.

This study provided the Lp(a) and LDL-c distribution levels and the risk categories for developing CVD in HIV positive individuals on HAART that could be used for future studies, for reference, estimation of the magnitude of

health problem and for administrative and planning purposes.

Materials and Methods

This was a cross sectional laboratory based study conducted at Livingstone General Hospital Laboratory between December, 2014 and February, 2015.

Convenience sampling was employed when selecting HIV seropositive individuals as they reported for routine medical tests at the Laboratory. Samples were selected, serum separated and stored at – 20 ^{0}c as they came. A total of 143 samples were collected and analyzed on Beckman Coulter AU480 analyzer. The study participant's age was ranging from 18-45 years consisting of HIV positive patients on HAART for one to ten years. Participants with any record of Withdrawal from combination ART, those on Protease Inhibitors, cigarette smoking, hypertension, diabetes mellitus, Cholestatic liver diseases, kidney failure, nephrotic syndrome, Hypothyroidism, hyperthyroidism, chronic consumption of alcohol, administration of niacin or nicotinic acid, Women with repeated abortions, pregnancy, treatment with carbamazepine or sodium valproate were excluded from the study. Clinical and demographic data was collected from patient files and laboratory forms using a data collection form.The Randox dedicated Lp(a) reagents[24] shipped from Northern Irelandwere used on Beckman coulter AU480 and for LDL- reagents, we used the manufacturer's (Beckman coulter) product purchased from South Africa using a local agent.

Data analysis

SPSS v.17 and STATA v.12 were used for data analysis. Descriptive statistics were used to obtain means, standard deviations etc. as well as for generating figure 1 and 2.

For Inference, ANOVA, student's T test, chi-square and Logistic regression were used and at 95% confidence interval, p <0.05 were considered significant.

The internationally (WHO expert committee, international federation of clinical chemistry etc) accepted CVD risk categories based on Lp(a) concentration[25]was used, namely; no risk for CVD =Lp(a) <14mg/dL; low risk = Lp(a) 14-29mg/dL; high risk = Lp(a) 30-49mg/dL; very high risk = Lp(a) ≥ 50mg/dL. Cut off value denoting high Lp(a) concentration used in this study was ≥ 30mg/dL, this is in accordance with data from prospective studies showing a higher cardiovascular risk in patients with Lp(a) levels >30 mg/dL[21,26-28].

Ethical considerations

The study was undertaken after ethical approval from the University of Zambia Biomedical Research Ethics Committee (UNZABREC) Assurance No. FWA00000338 IRB00001131 of IORG0000774, REF No. 007-10-14 obtained on the 12th of December, 2014. Permission was sought and granted from Livingstone General Hospital Management for the use of clinical samples and before data collection was started. All data collected was de-identified.

Findings

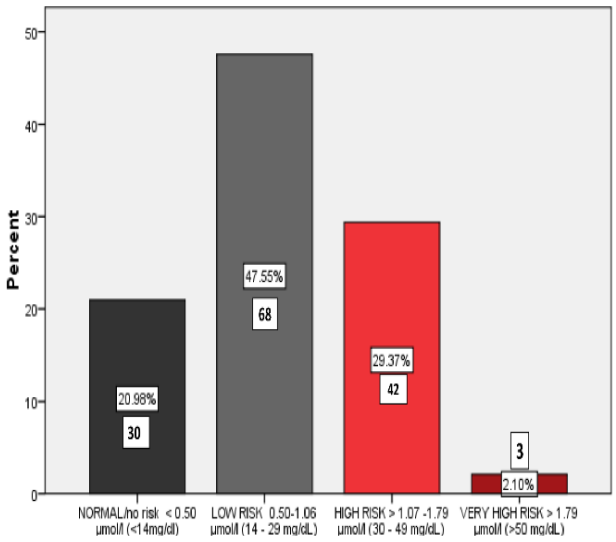

Fig. 1 Bar chart showing the participant's risk category for developing a cardiovascular disease based on their Lp(a) serum concentration levels *Reference values adopted from Ryan, GM and Julius, T (2005)*

Risk category for developing a CVD using a Lp(a) conc. threshold of 14mg/dL

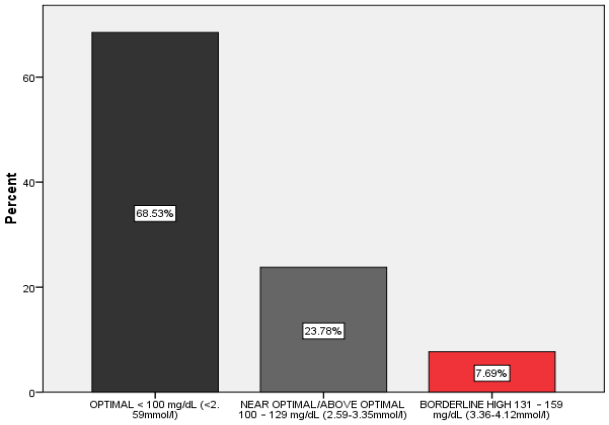

Fig. 2 Bar chart showing the participant's risk category for developing a cardiovascular disease according to their LDL-c levels.

Adopted from National Cholesterol Education Program (NCEP) (2001)[32].
Risk category for developing a CVD using a LDL-c threshold of 3.36mmol/l.

Table 1. Factors Predicting High Lipoprotein(a) in the study usingunivariate and multivariate logistic regression

Variable	Odds Ratio[u] (95% CI)	p-value	adjusted Odds[m] Ratio OR(95%CI)	p-value
Sex				
Male	1.00		1.00	
Female	0.99 (0.48,2.04)	0.982	0.62 (0.26,1.50)	0.297
Age category(in years)				
18-24	1.00		1.00	
25-31	8.18 (0.95,70.44)	0.056	10.14 (0.89,115.03)	0.062
32-38	9.09 (1.11,74.16	0.039*	11.47 (1.06,124.04)	0.045*
39-45	17.39 (2.13,141.33)	0.008*	16.32 (1.46,181.98)	0.023*
Duration category (in years)				
1-5 years	1.00		1.00	
6-10 years	4.33 (2.04,9.15)	<0.001 *	4.00 (1.66,9.64)	0.002*
ART combination				
TDF/FTC/EFV	1.00		1.00	
TDF/FTC/NVP	2.08 (0.74,5.82)	0.161	1.20 (0.39,3.65)	0.738
D4T/3TC/NVP	0.65 (0.13,3.25)	0.602	0.39 (0.06,2.32)	0.306
AZT/3TC/NVP	5.21 (1.21,22.29)	0.026*	9.02 (1.41,57.54)	0.020*
D4T/3TC/EFV	0.65 (0.06,6.08)	0.707	0.69 (0.05,8.75)	0.780
Low LDL-c	1.00		1.00	
High LDL-c	1.26 (0.35,4.57)	0.716	1.10 (0.24,4.90)	0.895

U= univariate logistic regression was used; m= multivariate logistic regression was used; * = statistically significant ; TDF= tenofovirdisoproxilfumarate; FTC= emtricitabine; EFV=efavirenze;NVP=nevirapine; D4T= stavudine; 3TC= lamivudine; AZT= zidovudine

Table 2: Demographic and clinical characteristics of the study population in comparison with mean Lp(a) and LDL-c concentrations .

characteristic		n (%)	Lp(a) mg/dL(range)	p-value	LDL-c mmol/l(range)	p-value
[tt]**Sex**						
	Male	57 (39.9)	24.6 (0.4,51.3)	0.719	2.23 (0.94,4.14)	0.078
	Female	86 (60.1)	23.9 (0.6,51.8)		2.43 (1.10,3.79)	
Total		143(100)				
[a]**Age category(years)**						
	18-24	21 (14.7)	16.1(0.6,41.5)	0.001*	2.26(1.10,3.54)	0.129
	25-31	31 (21.7)	23.4(0.6,48.5)		2.19(0.94,3.73)	
	32-38	48 (33.6)	23.8(0.4,48.9)		2.34(1.16,3.79)	
	39-45	43 (30.)	29.1(4.9,51.8)		2.53(1.41,4.14)	
[a]**Duration category (years)**						
	1-5	88 (61.5)	21.1(0.4,51.3)	<0.001*	2.32(0.94,4.14)	0.420
	6-10	55 (38.5)	29.2(2.7,51.8)		2.41(1.54,3.79)	
[a]**ART combination**						
	TDF/FTC/EFV	101 (70.6)	23.2(0.4,51.8)	0.136	2.34(0.94,4.14)	0.971
	TDF/FTC/NVP	18 (12.6)	28.4(2.7,48.9)		2.44(1.41,3.76)	
	D4T/3TC/NVP	10 (7.0)	22.4(12.6,39.7)		2.37(1.68,3.54)	
	AZT/3TC/NVP	9 (6.3)	31.3(11.3,46.3)		2.25(1.61,3.40)	
	D4T/3TC/EFV	5 (3.5)	18.1(7.0,30.0)		2.37(1.54,2.81)	

tt= two sample t test with equal variance was used to obtain p value; a= analysis of variance test was used; *= statistically significant; TDF= tenofovirdisoproxilfumarate; FTC= emtricitabine; EFV=efavirenze;NVP=nevirapine; D4T= stavudine; 3TC= lamivudine; AZT= zidovudine

Table 2 shows that there was no difference in the Lp(a) and LDL-c concentration means between males and females. It also shows that there was a significant association between age and Lp(a) concentration. Duration on ART was significantly associated with Lp(a) concentrations as well. All HAART combinations lead to increase in Lp(a) in the long term.

A correlation was done using Pearson's correlation in SPSS and the result showed a significant positive relationship between age $r(141) = 0.32$, $p<0.001$, duration on HAART $r(141) =0.43$, $p<0.001$ and Lp(a) concentration levels.

Pearson's correlation was used also to determine the relationship between age (as a continuous variable) and LDL-c concentration levels, the result showed a weak positive significant relationship $r(141) = 0.180$, $p= 0.031$.

Table 3: predisposing factors to high Lp(a) concentration

characteristics		n (%) high LP(a)level (≥30mg/dl)	Low Lp(a) level (<30mg)	p-value[c]
n		45(31.5%)	98 (68.5%)	
Sex				
	Male	18 (31.6)	39 (68.4)	0.982
	Female	27 (31.4)	59 (68.6)	
Age category(in years)				
	18-24	1 (4.8)	20 (95.2)	0.009*
	25-31	9 (29.0)	22 (71)	
	32-38	15 (31.3)	33 (68.8)	
	39-45	20 (46.5)	23 (53.5)	
Duration category	**(in years)**			
	1-5 years	17 (19.3)	71 (80.7)	<0.001*
	6-10 years	28 (50.9)	27 (49.1)	
ART combination				
	TDF/FTC/EFV	28 (27.7)	73 (72.3)	0.086
	TDF/FTC/NVP	8 (44.4)	10 (55.6)	
	D4T/3TC/NVP	2 (20)	8 (80)	
	AZT/3TC/NVP	6(66.7)	3(33.3)	
	D4T/3TC/EFV	1 (20)	4 (80)	

*= statistically significant; C= Chisquared test was used; TDF=tenofovirdisoproxilfumarate; FTC= emtricitabine; EFV=efavirenze;NVP=nevirapine; D4T=stavudine; 3TC= lamivudine; AZT= zidovudine

As shown in table 3, there was no association between having high Lp(a) levels and sex but high Lp(a) levels were more prevalent with age and increased duration on HAART. Specific ART combination was not associated with increased Lp(a), all combinations led to high Lp(a) in the long term

Table 4: comparison of LDL-c concentration below or above normal with the independent variables

Independent variable	n (%) high LDL-c concentration (≥3.36mmol/l)	Low LDL-c concentration (<3.36mmol/l)	p-value[c]
n	11(8%)	132(92.3%)	
Sex			
Male	3 (5.3)	54 (94.7)	0.375
Female	8 (9.3)	78 (90.7)	
Age category(in years)			
18-24	1 (4.8)	20 (95.2)	0.618
25-31	1 (3.2)	30 (96.7)	
32-38	5 (10.4)	43 (89.6)	
39-45	4 (9.3)	39 (90.7)	
Duration category (in years)			
1-5 years	6 (6.8)	82 (93.2)	0.620
6-10 years	5 (9.1)	50 (90.9)	
ART combination			
TDF/FTC/EFV	8 (7.9)	93 (92.1)	0.943
TDF/FTC/NVP	1 (5.6)	17 (94.4)	
D4T/3TC/NVP	1 (10)	9 (90)	
AZT/3TC/NVP	1 (11.1)	8 (88.9)	
D4T/3TC/EFV	0(0.0)	5(100.0)	

*= statistically significant; C= Chisquared test was used; TDF=tenofovirdisoproxilfumarate; FTC= emtricitabine; EFV=efavirenze;NVP=nevirapine; D4T=stavudine; 3TC= lamivudine; AZT= zidovudine

As shown in table 4, there was no difference between having high LDL-c levels and sex, age, duration on HAART or type of ART combinations.

Results and Disussion

Risk category for developing CVD using Lp(a) and LDL-c concentration levels.

As shown in figure 1, 79% of the participants were at risk for CVD based on Lp(a) levels , however, of these, 48% were at low risk (Lp(a) concentration levels ranging from 14-29mg/dL); 29% at high risk (Lp(a) levels ranging from 30-49mg/dL) and 2% very high risk (Lp(a) ≥ 50mg/dL).

As for LDL-c, as shown in figure 2, only 8% were in the borderline high risk category (LDL-c concentration from 3.36-4.12mmol/l), 68% of the total population were in the optimal category (LDL-c concentration < 2.59mmol/l) and 24% were in the near optimal/above optimal category (LDL-c concentration from 2.59-3.35mmol/l). There were no participants in the high category (LDL-c concentration from 4.14-4.90mmol/l) and very high category with LDL-c concentration levels above 4.92mmol/l.

Studies, on the risk categories for developing CVD based on Lp(a) and LDL-c in HIV positive patient on HAART are scarce. There is little data in literature of any studies that have reported risk categories for developing CVD using Lp(a) concentration levels. This may be one of the few studies to report this. As seen from the high percentage at risk for CVD above, Lp(a) determination is important to be conducted periodically in HIV positive patients on HAART.

Factors Predicting High Lp(a) in the study population

Age and duration on HAART

Using univariate and multivariate logistic regression (table 1), it was shown that the level of Lp(a) were likely to be higher as age advanced. Using the adjusted ratios in multivariate logistic regression, participants aged 32-38 yearswere 11 (95% CI[1.06,124.04]) times more likely to have high Lp(a) levels and ages 38-45 years were 16 (95%CI[1.46,181.98]) times more likely to have high Lp(a) levels than the participants in the age category 18-24 years which was the reference group. A correlation that was done using Pearson's correlation in SPSS showed a significant positive relationship between age r(141) = 0.32, p<0.001, duration on HAART r(141) =0.43, p<0.001 and Lp(a) concentration levels.

Using univariate logistic regression, the participants who were on HAART for longer duration (6-10 years) were 4 (95% CI[2.04,9.15]) times more like to have high Lp(a) levels compared to the reference group who were on HAART only for 1-5 years (p<0.001). Further adjusted for confounding and when combined with other factors, the group on HAART for 6-10 years were 4 (95%CI[1.66,9.64]) times more likely to have high Lp(a) levels compared to the participants on HAART for 1-5 years, p=0.002.

We were able to show that age and duration on HAART were significant predictors and factors associated with high Lp(a) level thereby indirectly increasing the risk for CVD in patients on HAART. The findings were similar to those reported in other studies[13, 12] were they reported that participants who where on HAART for 12 months had higher Lp(a) levels (54.8mg/dL ± 34.2) compared to the group treated for six months (39.9mg/dL ± 25.6) (p=0.034).They also reported that an increase of Lp(a) with age (p=0.025) was found particularly in the group of 35 to 50 years (58.7 ± 33.5 mg/dL). We therefore recommend baseline Lp(a) checks before initiating patients on HAART and periodic analysis to improve patient care and enhance preventive treatment in order to reduce CVD events.

There was no association between age category (p=0.618), duration on HAART (p=0.620) and having high (≥ 3.36mmol/l) LDL-c levels. This was contrary to a study done in Zambia[29]assessing the early effects of combination antiretroviral therapy (cART) on CVD risk markers where they reported a significant increase in LDL-c (P=0.02) in the group on D4T +3TC +NVP after three months of treatment. The same was reportedin another study[30]. However, in the current study, when

Pearson's correlation was used to determine the relationship between age (as a continuous variable) and LDL-c concentration levels, the result showed a weak positive significant relationship r(141) = 0.180, p= 0.031. The differences can be explained by the transformation or use of the categorical variable 'high LDL-c' for LDL-c which reduces the power of statistical test used. But when used as a continuous variable as shown by the Pearson's correlation, there is a significant positive association between LDL-c levels and age. However, the differences in LDL-c may be hard to explain as the study was limited. Some information like participant's diet, life style which has an impact on LDL-c was not obtained to ascertain why the distribution was like that.

Sex

Results showed that being male or female was not associated with high Lp(a) levels. There was no difference between sex and mean Lp(a) as shown in table 2. This is similar to the report in another study[13](p=0.34), probably due to 90% individual genetic predisposition of Lp(a) levels[7].

There was no significant association between sex (p=0.375) and having high (≥ 3.36mmol/l) LDL-c levels (table 4). However, the mean LDL-c levels in men (2.23mmol/l) were lower than those of females (2.43mmol/l) which is similar to another study[3] were they reported that the females had proportionally raised LDL-c slightly higher when compared to males (23.7% males had LDL-c ≥3.36mmol/l while 38.7% females had LDL-c ≥ 3.36mmol/l).In this current study 5.3% out of 55 males had LDL-c ≥ 3.36mmol/l and 9.3% out of 88 females had LDL-c ≥ 3.36mmol/l.

HAART combinations

In this study, Factors predicting high Lp(a) in the study population and hence increased risk to CVD there was no correlation between type of ART combination and mean Lp(a) concentration levels (p=0.136) as shown in table 2 and there was no Specific ART combination associated with raised Lp(a) concentrations (p= 0.086) (table 3) though the group receiving AZT+3TC+NVP (6.3%) were 9.02 (AOR) (95% CI[1.41,57.54]) times more likely to have high Lp(a) levels compared to the group receiving TDF+FTC+EFV (70.6%) and this was a significant finding in the research, p= 0.020 (table 1). All combinations increased Lp(a) in the long term as reported also in another study[12].

There was no association between ART combination (p=0.943) and having high (≥ 3.36mmol/l) LDL-c levels (table 4). This was contrary to another study[31] were they reported that some antiretroviral drugs, such as stavudine (d4T) increased the blood levels of LDL-cholesterol. Nevirapine (NVP) use was associated with increases in LDL-cholesterol as well[30]. This difference in the finding can be attributed to the fact that in our study, a combined analysis (ANOVA) was employed for ART combination and not for each specific combination (within groups). Also, logistic regression was not analyzed to determine the contribution of specific ART combinations in predicting high LDL-c levels.

LDL-c

The odds of having high Lp(a) serum levels in participants with High LDL-c levels was 1.10 (95%CI[0.24,4.90]) times compared to those with low LDL-c but as shown in table 1, this finding was not significant (P=0.895).

In this study, the levels of Lp(a) concentration were not associated with LDL-c levels (p=0.716) because Lp(a) is 90% genetically determined.

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