

Prognostic Value of Serum Lipoprotein (a) and Apo lipoprotein-B in diabetics with Myocardial Infarction and Chronic limb Threatening ischemia.

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Abstract

Aim: Current clinical guidelines require that five indices (total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides and the total/HDL cholesterol ratio) be measured or calculated to assess the lipid-related risk of vascular disease. Recently, quantification of plasma Lp (a) and Apo-B was proposed as recent clinical markers that will allow better prediction of coronary and peripheral arterial disease. This study prospectively examined whether high levels of Lp (a) and Apo-B have a significant risk and prognostic value in type 2 diabetic patients with myocardial infarction and peripheral vascular disease

Subject and Methods: The patients included in the study were selected properly from outpatient clinics of Vascular Surgery Unit as well as Internal Medicine Department (Cardiovascular Unit), Mansoura University.

The patients were divided into 4 groups: Group I (n=15): Type 2 DM with no CAD and no PVD. Group II (n=15): Type 2 DM with history of myocardial infarction and No PVD. Group III (n=15): Type 2 DM with no history of myocardial infarction but have symptomatic PVD. Group IV (n=15): Type 2 DM with history of myocardial infarction and have PVD. Patients with acute illness or taking Niacin, Estrogen replacement or antibiotics were excluded. All patients were subjected to thorough history taking, cardiovascular and peripheral vascular system evaluation including BMI, ABI, ECG, Doppler US echocardiogram as well as peripheral vascular angiography. Laboratory evaluation of our patients included assessment of diabetic state, HbA1c, standard lipid profile parameters as well as evaluation of Lp (a) and Apo-B.

Results: Serum level of Lp(a) and Apo-B showed highly statistically significant results when comparing group I with any group of type 2 diabetic patients complicated with either MI or PVD ($P<0.001$). However, serum apo-B level was highly significant in those complicated with PVD ($P<0.001$), while serum Lp (a) was statistically higher in those having myocardial infarction ($P=0.03$).

Conclusions: Our study revealed that elevation of serum level of both Lp (a) and Apo-B were significantly correlated with occurrence of myocardial infarction and different grades of peripheral vascular insufficiency in type 2 diabetic individuals. However, increased serum level of Lp (a) showed higher significant prediction for occurrence of MI while, elevation of serum level of Apo-B predict more the occurrence of PVD among our patients. Evaluation of serum Lp (a) and Apo-B levels should be considered a new risk factor and

is of prognostic value for occurrence of vascular complications in type 2 diabetic patients. More population-based prospective studies are needed to answer the question definitively of whether Lp (a) and Apo-B levels are more predictive of CAD and PVD in type 2 diabetic individuals than the traditional lipid parameters.

Key words: *Lipoprotein (a); Apo-lipoprotein B; Myocardial infarction; Peripheral vascular disease.*

Abbreviations: ABI; ankle brachial index, BMI; body mass index, CAD; coronary artery disease, CFA; common femoral artery, CI; confidence interval, CV; cardiovascular, DM; diabetes mellitus, ECG; electrocardiogram, HbA1c; glycated hemoglobin, HDL-cholesterol; high-density lipoprotein cholesterol, LDL; low-density lipoprotein cholesterol, LV; left ventricular, LVM; left ventricular mass, MI; myocardial infarction, MR; magnetic resonance imaging, PVD; peripheral vascular disease, RID; Radial immunodiffusion, VLDL; very low-density lipoprotein.

Introduction

Current clinical guidelines require that five indices (total cholesterol, LDL-cholesterol, HDL-cholesterol, triglycerides and the total/HDL-cholesterol ratio) be measured or calculated to assess the lipid-related risk of vascular disease. Five are also targets of therapy and therefore all must be measured initially and at follow up (1).

Recently, quantitation of plasma LP (a), Apo-B was proposed as recent clinical markers that will allow better prediction of coronary artery and peripheral vascular disease. Assays for LP (a), Apo-B are widely available and are frequently done by commercial laboratories. These laboratories use methods that often result in good intra-laboratory reproducibility with coefficients of variation less than 4% (2, 3).

Lp (a) is an LDL-like lipoprotein containing a unique Apo lipoprotein called apo (a) which is similar to plasminogen in structure, plasma levels of Lp (a) are genetically determined, however, considerable ethnic and racial differences exist in the distribution of Lp(a) levels and it is an acute phase reactant and should not be quantitated within several weeks after an acute illness or surgical procedures (4,5).

Lp(a) has been shown as a risk factor for atherosclerotic disease such as ischemic heart disease, myocardial infarction, shock and peripheral arterial disease and it is thought to play a role in the etiology of coronary artery disease (CAD) and has been identified in much larger concentration in people with family history of early onset CAD (6,7).

Apo lipoprotein-B is the major Apo lipoprotein in chylomicrons, VLDL and LDL. Only one molecule of apo-B exists per lipoprotein particle, and thus the quantity of apo-B in fasting plasma is a measure of the number of LDL and VLDL (non-HDL-cholesterol). Therefore plasma apo-B levels may be a better assay of the concentration of atherogenic lipoprotein particles than are non HDL-cholesterol levels. There is evidence that it is associated with the development and progressive nature of peripheral vascular disease (8).

Individuals with peripheral vascular disease have increased risk of cardiovascular events and death adding to the burden placed on health care services. The prevalence of peripheral arterial disease (PAD) in patients with ischemic heart disease varies in different series from around 10-30% and patients with documented CAD are more likely to have PVD. Primary and secondary prevention strategies are therefore required to target risk factors of particular importance in the etiology of coronary and peripheral arterial disease (9).

Subjects and Methods

This study prospectively conducted from March 2016 to April 2019 examined whether high levels of serum LP (a), Apo-B are considered new risk factors and are of prognostic value in the development of PVD and myocardial infarction in type 2 diabetic patients.

Our patients were divided into 4 groups:

- Group I (n=15): Type 2 DM with no CAD and no PVD.
- Group II (n=15): Type 2 DM with history of myocardial infarction and no PVD.

- Group III (n=15): Type 2 DM with no history of myocardial infarction but who have symptomatic PVD.
- Group IV (n=15): Type 2 DM with history of myocardial infarction and who have PVD.

The patients of the studied groups were selected properly from outpatient clinics of Vascular Surgery Unit and Internal Medicine Department (Cardiovascular Unit), Mansoura University Hospital. All patients were assessed for risk factors associated with the development of cardiovascular complications with stress on cardiovascular examination and assessment of peripheral vascular insufficiency. Patients with acute illness or taking Niacin, Estrogen replacement or antibiotics were not included. All patients were subjected to:

I- Peripheral vascular evaluation:

a- Clinical evaluation:

- Thorough history taking.
- Examination of the legs, including neurological assessment.
- Patients with PVD were categorized with regard to the severity of the disease according to Rutherford categories into (10):
 1. Category 0: asymptomatic.
 2. Category 1: mild claudication.
 3. Category 2: moderate claudication.
 4. Category 3: severe claudication.
 5. Category 4: ischemic rest pain.
 6. Category 5: minor tissue loss (no healing ulcer, focal gangrene with diffuse pedal ischemia).
 7. Category 6: major tissue loss (extending above tars metatarsal level, functional foot no longer salvageable).
- Ankle brachial index (ABI) was done for group III and IV (n = 30).

b- MR angiography was done for groups III and IV (n=30) and they were classified according to TASC guidelines into: A, B, C and D according to level of the disease (aorta-iliac, femoro-popliteal, infrapopliteal) (11).

II- Cardiovascular system evaluation includes:

- Thorough history taking with special concentration upon CV risk factors.
- Blood pressure measurement as well as history of hypertension and anti-hypertensive medications if any.
- Body mass index (BMI) = weight (in kg) / height (m)².

- Standard 12-lead surface ECG to evaluate ST-T-wave changes and arrhythmia if present.
- Color Doppler echocardiography with special concentration upon LV mass and LV mass index, presence or absence of wall motion abnormalities and intracavitary thrombi or spontaneous echo contrast.
- The risk of smoking was evaluated by smoking index (12, 13).

III- Laboratory methods:

- Evaluation of the diabetic state was done by estimation of serum fasting and postprandial blood glucose concentration, HbA1c, urine analysis for proteinuria or micro albuminuria and standard lipid profile parameters.
- Lp (a) assay: estimation of serum Lp (a) was performed by Lp(a)-turbidimetry which is a quantitative turbid metric test for measurement of Lp(a) in human serum or plasma. Latex particles coated with anti-Lp (a) antibodies are agglutinated when mixed with samples containing Lp (a). The agglutination causes an absorbance change, dependent upon the Lp (a) content of the sample that can be quantified by comparison from a calibrator of known Lp (a) concentration.
- Apo-B is determined by Radial immunodiffusion (RID) which is based on the complexing of antigen and antibody to produce a visible precipitin ring. It is still a reference method to which new methods are compared. It depends on the formation of a precipitate between an antibody and its specific antigen by suspending one in a gel and letting the other migrate through it from a well. Multiple wells are often used. Sensitivities as low as 0.15 mg/ml can be achieved.

Statistical Methods

It was performed using the statistical package for social studies (SPSS) for windows software package release 17. Results were presented as median and confidence intervals unless otherwise stated. Student t-test and Chi-squared test were applied as appropriate. A P-value ≤ 0.05 was considered significant. This study was approved by our local Institutional Research and Ethics board. The Mann-Whitney U-test was used to evaluate difference in Lp (a), Apo-B serum level in different studied groups. For each patient, the fasting lipid profile was determined according to the recent Canadian Recommendation for management and treatment of dyslipidemia (14). One-Way ANOVA was used to compare the difference of log [Lp (a)] among myocardial infarction patients and Apo-B in peripheral vascular disease patients.

Results

Demographic criteria

Comparison of the four groups included in the study revealed that body mass index (BMI) was statistically significant between the studied groups except when comparing group II and group III with group IV. Ankle-brachial index (ABI) was also statistically significant between the studied groups except when comparing group I with group II. However, age distribution showed no statistical significance between the different groups (table I).

Laboratory criteria

The level of LDL-cholesterol concentration was statistically significant when comparing group I with group II ($P<0.001$), group I with group IV ($P<0.001$), group II with group III ($P<0.001$), group II with group IV and group III with group IV ($P=0.003$ and 0.004 , respectively). On the other hand, HDL-cholesterol was statistically significant when comparing group I with group II, group I with group III and group I with group IV with high statistical significance ($P<0.001$ for each). However, less statistical significance was found when comparing group II or group III with group IV ($P=0.002$). Comparison of serum HDL-cholesterol concentration between group II and group III was not significant ($P=0.07$).

Serum level of Lp(a) and apo-B showed highly statistically significant results when comparing group I (type 2 diabetic patients without myocardial infarction or PVD) with any group of type 2 diabetic patients complicated with either myocardial infarction or PVD ($P<0.001$). Serum apo-B level was highly statistically significant in those complicated with PVD ($P<0.001$), while serum Lp (a) is statistically higher in those having myocardial infarction ($P=0.03$) (table II & III).

Echocardiographic criteria

LVM and LVM index were statistically significant when comparing group I with the other groups ($P<0.001$) (table IV).

Table V describes the presentation of PVD ($n=30$) in groups III and IV. According to Rutherford categories six patients in group IV were categorized as 3 and 2 patients as 5 in Rutherford categories.

As regards location of the disease according to TASC classifications femoropopliteal disease was found in 12 patients in group III and 3 patients in group IV. Infrapopliteal disease was found in 3 patients in group III and 12 patients in group IV.

Table VI and VII show that Lp (a) was the most statistically significant predictor for occurrence of myocardial infarction in patients with type 2 diabetes ($P<0.001$) while, apo-B was less significant ($P=0.05$) in the multivariate logistic regression analysis. Also, serum apo-B elevation was the most statistically significant predictor for occurrence of PVD in patients with type 2 diabetes ($P<0.001$). However, Lp (a) elevation was of less significance ($P=0.04$).

Group	Variable	Age	BMI	ABI
GI	Mean	59.20	22.47	1.01
	SD	9.55	1.88	0.06
GII	Mean	58.43	35.13	0.99
	SD	9.5	3.96	0.07
GIII	Mean	61.87	26.47	0.67
	SD	8.18	3.42	0.10
GIV	Mean	60.27	35.80	0.56
	SD	8.80	2.51	0.10
P values				
GI vs GII		0.93	<0.001	0.3
GI vs GIII		0.41	0.001	<0.001
GI vs GIV		0.75	<0.001	<0.001
GII vs GIII		0.37	<0.001	<0.001
GII vs GIV		0.69	0.58	<0.001
GIII vs GIV		0.61	0.53	<0.02

Table I: Demographic data of the studied groups.

Group	Variable	TC	HDL	LDL	TG	HbA1c
Group I No MI No PVD N=15	Mean	193.80	43.13	114.60	183.53	6.35
	SD	15.15	3.11	14.71	19.52	0.47
Group II MI No PVD N=15	Mean	268.53	31.07	181.93	303.87	8.17
	SD	33.84	4.53	27.52	54.18	0.60
Group III No MI PVD N=15	Mean	200.73	33.53	104.27	363.40	8.05
	SD	16.99	2.36	19.83	77.85	0.67
Group IV MI PVD N=15	Mean	387.73	27.20	215.00	356.87	8.83
	SD	66.49	4.09	29.09	43.54	0.74
P values						
GI vs GII		<0.001	<0.001	<0.001	<0.001	<0.001
GI vs GIII		0.24	<0.001	0.11	<0.001	<0.001
GI vs GIV		<0.001	<0.001	<0.001	<0.001	<0.001
GII vs GIII		<0.001	0.07	<0.001	0.02	0.62

GII vs GIV	<0.001	0.02	0.003	0.006	0.012
GIII vs GIV	0.03	0.02	0.004	0.004	0.017

Table II: Laboratory data of the studied groups.

Group	Variable	Lp(a)	Apo-B
Group I No MI No PVD N=15	Mean	14.07	84.27
	SD	4.43	16.71
Group II MI No PVD N=15	Mean	34.13	114.67
	SD	4.84	12.55
Group III No MI PVD N=15	Mean	24.00	157.00
	SD	3.51	14.03
Group IV MI PVD N=15	Mean	34.07	162.40
	SD	4.42	8.98
P values			
GI vs GII		<0.001	<0.001
GI vs GIII		<0.001	<0.001
GI vs GIV		<0.001	<0.001
GII vs GIII		<0.001	<0.001
GII vs GIV		0.969	<0.001
GIII vs GIV		0.03	0.93

Table III: Lp (a) and Apo-B levels in the studied groups.

Groups		Rutherford category							Disease location according to TASC classification							
Group I (n=15)		0							0							
Group II (n=15)		0							0							
		0	1	2	3	4	5	6	Femoropoplit.				Infrapoplit.			
									A	B	C	D	A	B	C	D
Group III (n=15)	n.	0	3	6	4	2	0	0	8	3	0	1	2	1	0	0
Group IV (n=15)	n.	0	0	3	6	4	2	0	1	1	1	0	1	2	5	4

Table V: Peripheral vascular characteristics of the studied groups.

Parameters	95% CI	T-test	P value
Lp(a)	17.2-32.9	14.16	<0.001
Apo-B	39.0-69.4	18.3	0.05

No MI: n = 30

MI: n = 30

Table VI: Multivariate logistic regression analysis of MI on other variables with predictive value of lipoprotein parameters for myocardial infarction in patients with type 2 DM.

Group	Variable	LAD	EF	FS	LVM
Group I N=15	Mean	3.07	0.66	35.73	185.73
	SD	0.24	0.064	4.48	62.87
Group II N=15	Mean	3.93	0.513	26.67	293.13
	SD	0.36	0.083	4.62	60.88
Group III N=15	Mean	3.80	0.578	31.00	280.33
	SD	0.42	0.057	3.23	46.13
Group IV N=15	Mean	4.01	0.505	27.33	306.50
	SD	0.43	0.079	4.35	60.47
P values					
GI vs GII		<0.001	<0.001	<0.001	<0.001
GI vs GIII		<0.001	0.001	0.003	<0.001
GI vs GIV		<0.001	<0.001	<0.001	<0.001
GII vs GIII		<0.038	0.01	0.006	0.52
GII vs GIV		0.55	0.07	0.09	0.08
GIII vs GIV		0.53	0.08	0.06	0.09

EF: Ejection fraction; FS: Fractional shortening, LAD: Left atrial diameter; LVM;

Left ventricular mass.

Table IV: Echocardiographic data of the studied groups.

Parameters	95% CI	T-test	P value
Lp(a)	11.2-18.7	18.06	0.04
Apo-B	66.7-84.1	17.4	<0.001

No PVD: n = 30

PVD: n = 30

Table VII: Multivariate logistic regression analysis of PVD on other variables with predictive value of lipoprotein parameters for PVD in patients with type 2 DM

Discussion

Several large, prospective cohort studies have demonstrated that diabetes mellitus (DM) is associated with an increased risk of coronary and peripheral artery disease (15). It is well known that CAD is a manifestation of macroangiopathy in type 2 DM. Diabetic macroangiopathy is also often associated with hyperglycemia and dyslipidemia. The majority of cases of type 2 DM have dyslipidemia characterized by increased triglyceride levels and decreased high-density lipoprotein (HDL) cholesterol levels. Several studies have provided evidence that hypertriglyceridemia and triglyceride-rich lipoproteins play a key role in the pathogenesis of diabetic macroangiopathy and that dyslipidemia is an important predictor of CAD and mortality in patients with DM (16).

Traditionally, lipoproteins have been separated on the basis of their hydrated densities; the major density classes of lipoprotein particles include chylomicrons, very low-density lipoprotein (VLDL), intermediate-density lipoproteins, low-density lipoprotein (LDL), and high-density lipoproteins (HDL) (17). Chylomicrons are intestinal lipoproteins that transport dietary lipids to peripheral tissues and the liver. They are triglyceride-rich and contain one form of apolipoprotein B (apo-B), apo B-48. The triglycerides in chylomicrons are hydrolyzed by the endothelial enzyme lipoprotein lipase, which requires apolipoprotein C-II (apo C-II) as a cofactor (18). The process involves the binding of apolipoprotein E (apo E) on the chylomicron remnants to a putative hepatic remnant receptor (or apo E receptor) (19). Very low-density lipoproteins are triglyceride-rich lipoproteins secreted by the liver and contain another form of apo-B, apo-B-100.

Low-density lipoproteins transport cholesterol ester to various peripheral tissues, but a substantial amount of LDL is eventually removed from the circulation by the liver when apo B-100 is bound to the hepatic LDL receptor (20). Low-density lipoprotein can undergo oxidative modification, producing a form of oxidized LDL that can cause cholesterol loading in cells (21).

High-density lipoproteins are synthesized and secreted by the intestine and the liver and also are generated by hydrolysis of triglyceride-rich lipoproteins. The major Apo lipoproteins in HDL are apolipoprotein A-I (apo A-I) and apolipoprotein A-II (apo A-II). This may be one important route of human reverse cholesterol transport (22).

Apolipoprotein-B is the major apolipoprotein in chylomicrons, VLDL, intermediate-density lipoprotein, and LDL. Mutations in the

apo-B gene can cause low levels of apo-B and LDL cholesterol and may be associated with protection from premature coronary artery disease (23). Only one molecule of apo-B exists per lipoprotein particle, and thus the quantity of apo-B in fasting plasma is a measure of the number of LDL and VLDL particles. In fact, the plasma levels of “non-HDL cholesterol”, which includes both LDL and VLDL are correlated with plasma apo-B levels. Therefore, plasma apo-B levels may be a better assay of the concentration of atherogenic lipoprotein particles than are LDL-cholesterol or non-HDL cholesterol levels (24).

Lipoprotein (a) is an LDL-like lipoprotein containing a unique apolipoprotein called apo (a). Apolipoprotein (a) is similar to plasminogen in structure and may interfere with plasminogen activation. Plasma levels of Lp (a) vary across a 1000-fold range, and their distribution is skewed to the left in most populations. However, considerable ethnic and racial differences exist in the distribution of Lp (a) levels. Plasma Lp (a) levels are genetically determined. The apo (a) gene accounts for more than 90% of the variation in plasma Lp (a) concentrations. Lipoprotein (a) is also an acute-phase reactant, its levels increase in acute inflammatory states and after myocardial infarction and surgical procedures (25, 26).

The lack of standardization and reference methods for apolipoprotein assays is a limitation to the general application of apolipoprotein quantitation in clinical practice. Assays for apo A-I and apo-B are widely available and are frequently done by commercial laboratories. These laboratories use methods that often result in good intralaboratory reproducibility, with coefficients of variation within laboratories that are generally less than 4%. Several commercially available Lp (a) assay kits are used by research laboratories for Lp (a) quantitation. Lipoprotein (a) is an acute-phase reactant and should not be quantitated within several weeks after an acute illness or surgical procedure (27).

Our study revealed that elevation of serum level of both Lp (a) and apo-B were significantly correlated with occurrence of myocardial infarction and different grades of peripheral vascular insufficiency in type 2 diabetic individuals. However, increased serum level of Lp (a) showed statistically significant higher predictive value for occurrence of myocardial infarction and elevation of serum level of apo-B was found in those type 2 diabetic patients complicated with PVD. This issue was debatable in different clinical series (28, 29, and 30).

Multiple retrospective, cross-sectional studies comparing apo-B levels in patients with coronary artery disease with controls have been reported and have consistently found an association of plasma apo B concentrations with increased risk for premature coronary artery disease as well as PVD. Furthermore, a cross-sectional study in patients who had coronary artery bypass graft surgery determined that apo-B concentration was a better discriminator than LDL-cholesterol concentration in predicting recurrent atherosclerotic disease in bypass grafts 10 years after surgery (31).

Another prospective study found that apo-B levels were substantially associated with premature coronary artery disease by univariate analysis but were not more predictive than total cholesterol levels by multivariate analysis. After multiple logistic regression, the association of apo-B was independent of total cholesterol and triglyceride levels and overall, the apo B level was the most strongly associated with coronary and peripheral artery disease risk (32).

Nevertheless, recent larger cross-sectional studies supported the independent association of Lp (a) with premature coronary artery disease. Three studies evaluated the predictive value of Lp (a) levels in patients with established coronary artery disease after therapeutic intervention. In a cross-sectional study of 167 patients who had coronary artery bypass surgery, Lp(a) levels were independently correlated with coronary bypass saphenous vein graft stenosis ($P=0.002$) (33). Two studies that evaluated the predictive value of Lp (a) levels in restenosis after percutaneous transluminal coronary angioplasty produced conflicting results. In addition to coronary artery disease, retrospective studies showed that Lp (a) levels are associated with clinical cerebrovascular and peripheral vascular atherosclerosis and carotid artery wall thickness in asymptomatic persons (34).

The Quebec Cardiovascular Study demonstrated prospectively that hypertriglyceridemia hyper-apo B was associated with a threefold increase in the risk of vascular events, whereas hypertriglyceridemia with a normal apo B was not (35).

So our recommendation is that more population-based prospective studies are needed to answer the question definitively of whether apo-B levels are more predictive of premature coronary artery disease and PVD in type 2 diabetic patients than are traditional lipid parameters. In addition, prospective studies of Lp (a) and apo-B levels in targeted populations of patients with premature coronary artery disease or with family histories of premature coronary artery disease are required as well as those with PV insufficiency.

Patients who were treated aggressively with lipid-lowering therapy experienced less disease progression and fewer cardiovascular events than did controls treated with conventional therapy. Although many of these patients also had increased LDL-cholesterol concentrations, this suggests that intervention based on apo-B levels may be clinically beneficial (36).

Conclusions

Our study revealed that elevation of serum level of both Lp (a) and Apo-B were significantly correlated with occurrence of myocardial infarction and different grades of peripheral vascular insufficiency in type 2 diabetic individuals. However, increased serum level of Lp (a) showed higher significant prediction for occurrence of MI while, elevation of serum level of Apo-B predict more the occurrence of PVD among our patients. Evaluation of serum Lp (a) and Apo-B levels should be considered a new risk factor and is of prognostic value for occurrence of vascular complications in type 2 diabetic patients. More population-based prospective studies are needed to answer the question definitively of whether Lp (a) and Apo-B levels are more predictive of CAD and PVD in type 2 diabetic individuals than the traditional lipid parameters.

Recommendations

These data raise the possibility that at least for high risk patients with type 2 diabetes and hyperlipidemia follow up could be simplified and expenses reduced if only lipoprotein (a) and Apo-B were measured.

Apolipoprotein-B level can be decreased successfully with nicotinic acid (niacin), bile acid sequestrates (cholestyramine, colestipol), fibrates (gemfibrozil, fenofibrate), and hydroxymethylglutaryl coenzyme A reeducates inhibitors (lovastatin, pravastatin, simvastatin, fluvastatin). However, the only drug studies that reported reduction in LP (a) levels have used niacin, either alone or in combination with other drugs. Therefore, patients requiring drug treatment for elevated LDL cholesterol levels who also have elevated LP (a) levels should be considered for niacin therapy (37).

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