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Lipoprotein(a), Cardiovascular Disease, and Contemporary Management

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Abstract

Elevated lipoprotein(a) (Lp[a]) is a causal genetic risk factor for cardiovascular disease. To determine if current evidence supports both screening and treatment for elevated Lp(a) in high-risk patients, an English-language search of PubMed and MEDLINE was conducted. In population studies, there is a continuous association between Lp(a) concentrations and cardiovascular risk, with synergistic effects when low-density lipoprotein (LDL) is also elevated. Candidates for Lp(a) screening include patients with a personal or family history of premature cardiovascular disease, familial hypercholesterolemia, recurrent cardiovascular events, or inadequate LDL cholesterol (LDL-C) responses to statins. Given the comparative strength of clinical evidence, reducing LDL-C to the lowest attainable value with a high-potency statin should be the primary focus of lipid-modifying therapies. If the Lp(a) level is 30 mg/dL or higher in a patient who has the aforementioned characteristics plus residual LDL-C elevations (≥70-100 mg/dL) despite maximum-potency statins or combination statin therapy, the clinician may consider adding niacin (up to 2 g/d). If, after these interventions, the patient has progressive coronary heart disease (CHD) or LDL-C levels of 160-200 mg/dL or higher, LDL apheresis should be contemplated. Although Lp(a) is a major causal risk factor for CHD, no currently available controlled studies have suggested that lowering it through either pharmacotherapy or LDL apheresis specifically and significantly reduces coronary risk. Further research is needed to (1) optimize management in order to reduce CHD risk associated with elevated Lp(a) and (2) determine what other intermediate- or high-risk groups might benefit from Lp(a) screening.

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Elevated lipoprotein(a) (Lp[a]) is an independent, causal risk factor for atherosclerotic cardiovascular disease (CVD).[1-3] Discovered in 1963 by Kåre Berg's group, Lp(a) shares antigens with low-density lipoprotein (LDL)[4,5] but is much denser, overlapping the band for high-density lipoprotein (HDL).[6] This review (1) considers the biochemistry and potential pathophysiology of Lp(a), (2) surveys evidence linking *LPA* gene allelic variants and increased Lp(a) levels to increased cardiovascular (CV) risk, and (3) reviews potential screening and treatment strategies for the management of elevated Lp(a).

An English-language search of PubMed and MEDLINE dating from January 1, 1975, through March 1, 2012, was conducted. The title terms *lipoprotein(a)* and *Lp[a]* were joined with terms including **apo**, *atherosc**, **cardiovasc**, **cholest**, **coronary**, *heart disease*, **lip**, *myocardial infarction*, *risk factor*, and *stroke*. MeSH key terms included *human*, *drug therapy*, and *efficacy*. For the clinical section, randomized controlled trials (RCTs) were eligible for inclusion, whereas the clinical algorithm section included data from RCTs, epidemiological studies, and consensus treatment guidelines.

OVERVIEW OF BIOCHEMISTRY AND POTENTIAL PATHOPHYSIOLOGIC EFFECTS

Lipoprotein(a) includes a single molecule of apolipoprotein (apo) B_{100} covalently linked, in a 1:1 molar ratio, to apo(a). This unique glycoprotein-containing (hydrophilic) moiety is secreted by the liver.[7] The 2 molecules are most likely complexed in the hepatocyte cellular membrane and are connected biochemically by a disulfide bridge through cysteine residues within apo(a) (Cys4057) and apo B_{100} (Cys4326).[8]

Although Lp(a) contains an LDL–receptor binding region, the hepatic LDL receptor likely plays a negligible role in Lp(a) catabolism. Rather, levels of Lp(a) are determined chiefly by the rate of de novo hepatic synthesis (~5.0 mg/kg per day) (Figure 1). Catabolic pathways may include dissociation of apo(a) from apo B_{100}, formation of differing molecular-weight

fragments, and clearance largely by the kidney and spleen.[9]

Within apo(a) is a unique region highly structurally homologous to plasminogen but devoid of protease activity. By competitively antagonizing plasminogen binding, Lp(a) may have played an ancestral role in hemostasis and wound healing at sites of arterial injury, attenuating fibrinolysis, promoting thrombosis/coagulation, and delivering cholesterol. Potential atherogenic effects may include arterial deposition of oxidized phospholipids by apo B_{100}.[10]

POPULATION-BASED AND GENETIC EVIDENCE

Influence of Heredity on Lp(a) Structure, Levels, and CV Risk

Lipoprotein(a) levels are codominantly inherited. The *LPA* gene is located on chromosome 6 (6q26-27). Although typically stable within individuals over time, Lp(a) levels are highly heterogeneous across individuals and populations, including members of different races: some black populations have up to 4-fold higher median Lp(a) levels than their white counterparts.[11,12] Chief determinants of Lp(a) heterogeneity are the 30 different isoforms of apo(a), which are termed *kringles* because their biochemical structure resembles a Danish pastry. Each kringle contains approximately 80 amino acids and has a molecular weight of about 10 kDa.

The key *LPA* gene sequence that influences Lp(a) levels and atherogenicity is the number of kringle IV type 2 (KIV-2) repeats. This number largely determines the size of apo(a) and levels of Lp(a). Smaller numbers of KIV-2 repeats (ie, <22) are associated with higher levels of Lp(a) and potentially more atherogenic apo(a). Small apo(a) Lp(a) may be associated with higher Lp(a) levels because the smaller molecules are more readily synthesized in the liver and less readily degraded by cellular organelles.

In Europeans, a single-nucleotide polymorphism (SNP) in the *LPA* gene (rs3798220) was directly related to a small number of KIV-2 copies.[13] In white adults, carriers of the rs3798220 allele were at more than a 3-fold increased risk of severe coronary heart disease (CHD) (adjusted odds ratio, 3.14; 95% CI, 1.51-6.56) and had more than a 5-fold increased median plasma Lp(a) level compared with noncarriers ($P<.004$).[13,14]

ARTICLE HIGHLIGHTS

- Lipoprotein(a) (Lp[a]) is an independent, causal risk factor for atherosclerosis that is highly heritable.
- Each molecule of Lp(a) contains a single molecule of apolipoprotein (apo) B and a single apo(a) moiety secreted by the liver. Apo(a) moieties are biochemically heterogeneous, and a profile of predominantly smaller apo(a) isoforms is associated with higher cardiovascular (CV) risk.
- Epidemiological evidence supports a continuous association between Lp(a) cholesterol levels and CV risk, with a steeper risk gradient when both Lp(a) and low-density lipoprotein cholesterol (LDL-C) are elevated (ie, "multiplier effect").
- Certain single-nucleotide polymorphisms of the *LPA* gene allele—rs10455872 and rs3798220 in whites and rs9457951 in blacks—may be associated with higher population CV risk levels.
- Patients with both Lp(a) cholesterol levels above 30 mg/dL and Lp(a) particle levels (lipoprotein) above 72 nmol/L may be at particularly pronounced atherothrombotic risk and hence may warrant more intensive lipid-altering (and/or aspirin antiplatelet) therapy. However, even in the presence of elevated Lp(a), the first treatment target of lipid-altering therapy should be LDL-C, not Lp(a).

A second key gene sequence is the number of pentanucleotide (PN) repeats within the 5′ control region of the *LPA* gene. Allelic variants in the PN segment are in linkage disequilibrium with those in the KIV-2 sequence. In one study, the presence of KIV-2 allelic variants explained 9.7% of between-patient variance in Lp(a) levels, the PN allelic variant explained 3.5%, and the combination explained 19%.[15]

LPA Gene SNPs and Risks of CVD

Supportive evidence for associations between SNPs of the *LPA* gene and increased Lp(a) levels (and/or elevated CHD risk) include data from Mendelian randomization studies and other investigations.[16-20]

Concurrence of 2 SNPs of the *LPA* gene—rs10455872 and rs3798220—accounted for 36% of the variance in Lp(a) concentrations among those of European descent within the Precocious Coronary Artery Disease Investigation (PROCARDIS).[16,21] Among African Americans,

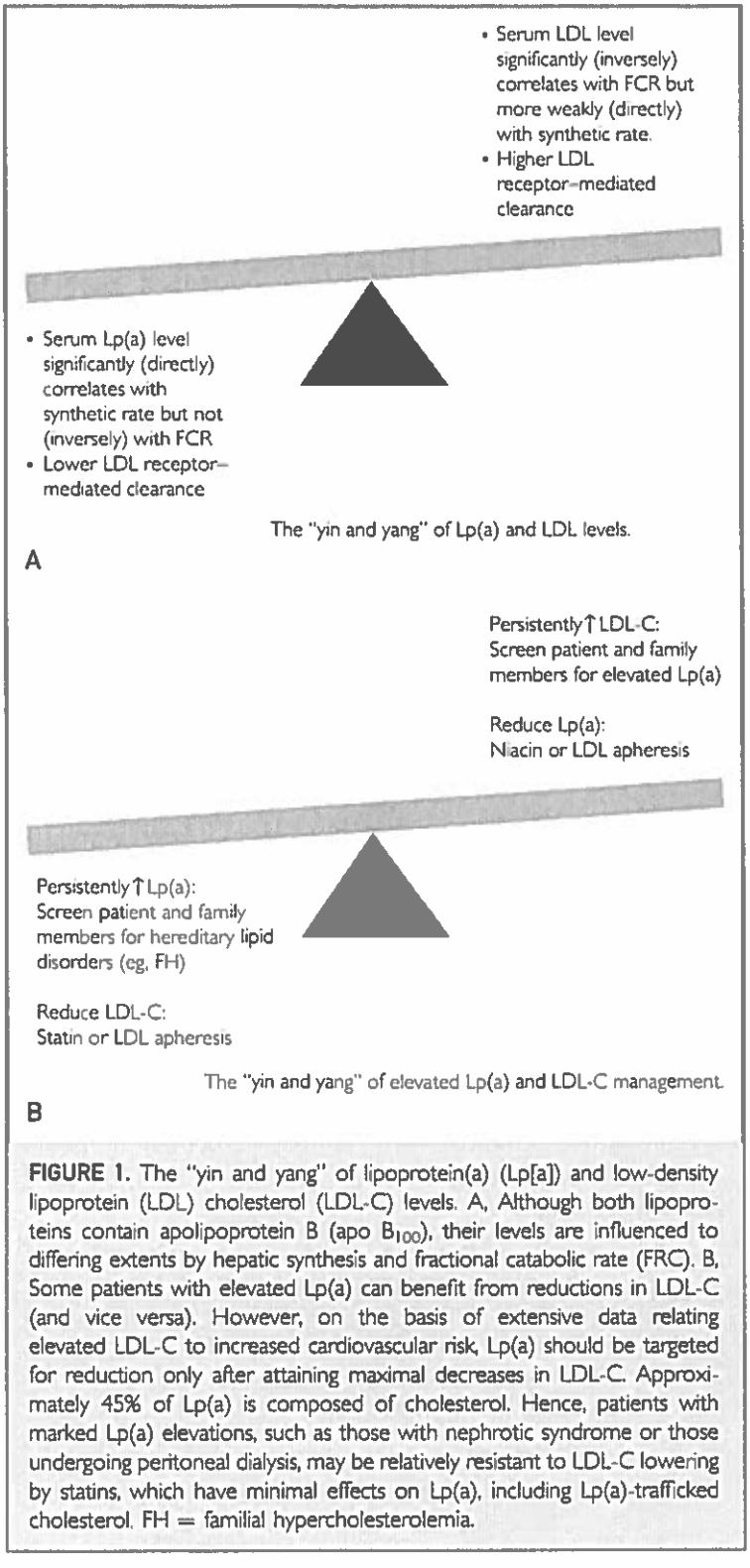

FIGURE 1. The "yin and yang" of lipoprotein(a) (Lp[a]) and low-density lipoprotein (LDL) cholesterol (LDL-C) levels. A, Although both lipoproteins contain apolipoprotein B (apo B_{100}), their levels are influenced to differing extents by hepatic synthesis and fractional catabolic rate (FRC). B, Some patients with elevated Lp(a) can benefit from reductions in LDL-C (and vice versa). However, on the basis of extensive data relating elevated LDL-C to increased cardiovascular risk, Lp(a) should be targeted for reduction only after attaining maximal decreases in LDL-C. Approximately 45% of Lp(a) is composed of cholesterol. Hence, patients with marked Lp(a) elevations, such as those with nephrotic syndrome or those undergoing peritoneal dialysis, may be relatively resistant to LDL-C lowering by statins, which have minimal effects on Lp(a), including Lp(a)-trafficked cholesterol. FH = familial hypercholesterolemia.

the *LPA* gene allelic variant most strongly associated with Lp(a) levels was rs9457951[20]; its presence explained about 5% of the variance in Lp(a) levels.

EPIDEMIOLOGICAL EVIDENCE ASSOCIATING ELEVATED Lp(a) WITH INCREASED CV RISK

Table 1 summarizes findings relating elevations in Lp(a) cholesterol (Lp[a]-C) to increased CV risk in diverse populations, including individuals of different sexes, ages, and races.[1,3,22-27] Potential conclusions from these epidemiological studies included the following:

- There is an independent, continuous association between elevated Lp(a) and CV risk that is statistically significant, although of lower magnitude, compared with associations of elevated LDL cholesterol (LDL-C) with risk
- Associations of Lp(a) with CV risk exhibit "multiplier effects"; the risk gradient per increment in Lp(a) is steeper in the presence of markedly elevated LDL-C
- Lp(a) levels vary 500- to 1000-fold (vs 2- to 5-fold for LDL-C)
- Distributions of Lp(a) levels are skewed; medians tend to be lower than means and more useful in characterizing population levels
- Higher proportions of African Americans exhibit Lp(a) levels of at least 30 mg/dL (to convert to µmol/L, multiply by 0.0357) (68% vs 26% of whites[26]). Although African Americans may not experience an equally elevated CHD risk per increase in Lp(a) compared with whites (possibly because of lower prevalences of small apo[a] isoforms, as well as lower LDL-C and higher HDL cholesterol [HDL-C] levels in African Americans), elevated Lp(a) confers significant increased CHD risk[22,29-31]
- Associations between elevated Lp(a) and CHD in women are less robust than in men, possibly because of the cardioprotective and vasoprotective effects of endogenous estrogen in premenopausal women. In women, elevated Lp(a) may function as a stronger risk factor when combined with elevated inflammatory or thrombotic markers: in the Nurses' Health Study, an Lp(a)-C level of at

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least 30 mg/dL, in combination with elevated fibrinogen (≥400 mg/dL [to convert to μmol/L, multiply by 0.0294]) or C-reactive protein (≥3 mg/L [to convert to nmol/L, multiply by 9.524]) levels, placed women at more than 3-fold increased relative CHD risk (vs lower values of each pair of factors/markers).[18,32,33]

Lp(a) LEVELS AND CV RISK IN MAJOR CLINICAL OUTCOMES STUDIES

Most landmark RCTs reporting that lipid therapies decreased CV risk—including the influential Coronary Drug Project[34,35]—did not report treatment effects on Lp(a) or reported that Lp(a) levels did not predict coronary events.[36]

Scandinavian Simvastatin Survival Study

In the Scandinavian Simvastatin Survival Study (4S)[4] subgroup analysis in 4402 high-risk men with CHD, markedly elevated LDL-C, and data on Lp(a), results were compared in patients within the upper half of the Lp(a) distribution (Lp[a] >91.1 U/L) with those in the lower half of the distribution. Findings included the following:

- Numbers of deaths were significantly lower in the bottom (192 deaths) vs the top (240 deaths) half of the Lp(a) distribution in the simvastatin and placebo groups combined ($P<.05$)
- Numbers of coronary events were significantly lower in the bottom (487 patients with MCE events) vs the top (555 patients with MCE events) half of the Lp(a) distribution in both treatment groups combined ($P<.03$)
- Baseline Lp(a) concentrations were significantly (directly) predictive of both (1) mortality in the simvastatin group ($P=.013$) and (2) coronary events in each treatment group ($P\leq.010$) in adjusted logistic regression analyses.

Familial Atherosclerosis Treatment Study

In the Familial Atherosclerosis Treatment Study (FATS),[37] a post hoc analysis revealed a correlation between on-treatment Lp(a) levels and atherosclerotic progression, with an interaction between Lp(a) and LDL-C reductions. The baseline mean Lp(a) level of approximately 35 mg/dL and median Lp(a) level of 20 mg/dL were consistent with the expected skewed distribution for this lipoprotein. Among 120 participants completing the study, changes from baseline in Lp(a) included an 11.4% reduction in the conventional therapy group (placebo), a 9.9% decrease in a bile acid resin–lovastatin arm, and a 25.8% decline in the bile acid resin–niacin arm.[38]

There was a sharp increase in CHD incidence over the serum Lp(a) range of 24 to 36 mg/dL (Figure 2). However, changes in Lp(a) were not independently predictive of atherosclerotic lesion regression. Lipoprotein(a) levels emerged as the best correlates to baseline CHD severity ($r=0.30$; multivariate adjusted $P<.001$). There was an interaction between changes in LDL-C and in Lp(a): when LDL-C decreased modestly, on-treatment Lp(a) levels were important CHD correlates. However, when LDL-C decreased markedly, "persistent elevations of Lp(a) were no longer atherogenic or clinically threatening."[37]

HDL-Atherosclerosis Treatment Study

As in the FATS, the incidence of CHD in the HDL-Atherosclerosis Treatment Study (HATS)[39] increased in the same direction as changes in Lp(a), albeit more sharply and over a narrower range of Lp(a) values (Figure 2). The baseline mean Lp(a) level ranged from 21 to 30 mg/dL in different treatment groups. Lipoprotein(a) decreased from baseline by 14.8% (from 27 to 23 mg/dL) in the niacin-statin group compared with 3.4% with placebo (from 30 to 29 mg/dL). The study did not report correlations between changes in Lp(a) and either percent stenosis or CV event incidence.[39]

Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health Outcomes

The Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health Outcomes (AIM-HIGH)[40] RCT evaluated the hypothesis that increasing HDL-C (and improving other lipid/lipoprotein end points) would confer significantly enhanced cardioprotective effects compared with control of LDL-C alone. Although Lp(a) decreased by 24.9% with extended-release niacin (1.5-2.0 g) combined with simvastatin (40-80 mg) vs 6.4% with

TABLE 1. Summary of Lipoprotein(a) (Lp[a]) Levels and Cardiovascular Disease (CVD) Risk in Epidemiological Studies[a,b]

Reference, year	Population	Lp(a)-C level (mg/dL)	CVD risk	Other risk relationships	Comment
Virani et al,[22] 2012					
CVD, prospective cohort	13,318 Racially representative (26% African American) US adults aged 45-64 y initially without CVD followed up for 20 y	African Americans: Highest (>24) vs lowest (≤6.1) quintile Whites: Highest (>13.5) vs lowest (≤1.5) quintile	African Americans (highest vs lowest): HR, 1.35; 95% CI, 1.06-1.74 Whites (highest vs lowest): HR, 1.27; 95% CI, 1.10-1.47	Per 1-SD increase in log-Lp(a) (0.90 mg/dL for African Americans and 1.15 mg/dL for whites): 13% increase in relative CVD risk in African Americans (HR, 1.13; 95% CI, 1.04-1.23); 9% increase in relative CVD risk in whites (HR, 1.09; 95% CI, 1.04-1.15)	"[E]levated Lp(a) levels were associated with incident CVD in blacks…and this risk was comparable to that in whites. Elevated Lp(a) should therefore be considered a risk factor for CVD in blacks."[22] Risk for incident CVD was graded but statistically significant only for the highest compared with the lowest Lp(a) quintile
Ischemic stroke, as above	As above	>30 vs ≤10	African Americans: Adjusted HR for ischemic stroke, 2.12; 95% CI, 1.48-3.03 Whites: Adjusted HR for ischemic stroke, 1.65; 95% CI, 1.04-2.61	African Americans: Adjusted HR for ischemic stroke in upper (>24 mg/dL) vs lower (≤6.1 mg/dL) Lp(a) quintiles, 1.60; 95% CI, 1.10-2.34 Whites: Adjusted HR for ischemic stroke in upper (>13.5 mg/dL) vs lower (≤1.5 mg/dL) Lp(a) quintiles, 1.27; 95% CI, 0.92-1.76 Women: Adjusted HR in upper (18.6 mg/dL) vs lower (≤2.1 mg/dL) Lp(a) quintiles, 2.07; 95% CI, 1.41-3.03 Men: Adjusted HR in upper (>15.2 mg/dL) vs lower (≤1.7 mg/dL) Lp(a) quintile, 1.50; 95% CI, 1.05-2.14	Adjusted HR for incident ischemic stroke greater in African Americans, who also tended to have higher Lp(a)-C levels (upper quintile >24 mg/dL) vs whites (upper quintile >13.5 mg/dL). Women also tended to have higher Lp(a) levels: upper quintile, 18.7-81.7 mg/dL vs 15.3-80.3 mg/dL in men
Emerging Risk Factors Collaboration,[23] 2009; meta-analysis of 36 prospective cohort studies	126,634 Participants with no BL history of CHD or stroke. Predominantly Europeans and North Americans	Upper tertile of BL Lp(a) Lower tertile of BL Lp(a)	CHD (adjusted), 5.6/1000 PY CHD (adjusted), 4.4/1000 PY	Adjusted HR for CHD, 1.13 (95% CI, 1.09-1.18) per 3.5-fold higher Lp(a) Adjusted HR for ischemic stroke, 1.10 (95% CI, 1.02-1.18) per 3.5-fold higher Lp(a)	"Under a wide range of circumstances, there are continuous, independent, and modest associations of Lp(a) concentrations with risk of CHD and stroke. Further studies are needed in nonwhite racial groups, particularly blacks and South Asian populations, which have different Lp(a) concentrations."[23]
Bennet et al,[1] 2008; case-control study	2047 Adults with incident MI or CHD death followed up for 19 y and 3921 controls	>14.9 vs <4.2 (upper vs lower tertile)	Adjusted OR for CHD, 1.61; 95% CI, 1.41-1.84	Model adjusted for age, sex, and period of recruitment OR for CHD, 1.77 (95% CI, 1.57-1.99) for upper vs lower Lp(a) quintile OR for CHD, 1.23 (95% CI, 1.16-1.31) for log-Lp(a) >1 SD OR for CHD, 1.45 (95% CI, 1.32-1.58) for upper vs lower Lp(a) tertile in meta-analysis of 31 prospective studies	ORs for CHD were smaller per increments in Lp(a) vs total cholesterol. Further research is needed to determine if the graph of relative CHD risk vs BL Lp(a) is linear or curvilinear "Levels of Lp(a) are highly stable within individuals across many years…."[1]

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TABLE 1. Continued

Reference, year	Population	Lp(a)-C level (mg/dL)	CVD risk	Other risk relationships	Comment
Kamstrup et al,[14] 2008; prospective cohort study	9330 Adults initially free of CHD followed up for 10 y	vs <5: 5-29 30-84 85-119 ≥120 vs <5: 5-29 30-84 85-119 ≥120	Women (HR for MI): 1.1 (95% CI, 0.6-1.9) 1.7 (95% CI, 1.0-3.1) 2.6 (95% CI, 1.2-5.9) 3.6 (95% CI, 1.7-7.7) Men (HR for MI): 1.5 (95% CI, 0.9-2.3) 1.6 (95% CI, 1.0-2.6) 2.6 (95% CI, 1.2-5.5) 3.7 (95% CI, 1.7-8.0)	For each 10-mg/dL increase in Lp(a), significant 6%-9% increase in relative risk of CHD For each log-SD increase, significant 12%-17% increase in relative risk of CHD	"Multiplier effect": Absolute 10-y CHD risk increases sharply when Lp(a) is extremely elevated and other risk factors are present Absolute 10-y MI risk in hypertensive female smokers aged >60 y with Lp(a) ≥120 vs <5 mg/dL: 20% vs 10% Corresponding data in men: 35% vs 19%
Suk Danik et al,[3] 2006					
CHD, prospective cohort study	27,791 Initially healthy middle-aged (≥45 y) US women followed up for 10 y	Upper quintile median (65.5) vs lower quintile median (1.9)	Adjusted HR for CHD, 1.35; 95% CI, 1.07-1.71; $P<.001$ for trend Adjusted HR for ischemic stroke, 1.87; 95% CI, 1.29-2.71; $P=.003$ for trend	Moderate but significant correlation between Lp(a) and apo B or LDL-C levels Multiplier effect: HR is increased most when LDL-C is >121 mg/dL (median) and Lp(a) is >90th percentile; HR, 1.81; 95% CI, 1.48-2.23	Multiplier effects. "[E]xtremely high levels of Lp(a) (≥90th percentile)...were associated with increased cardiovascular risk, particularly in women with high levels of LDL-C....the threshold and interaction effects observed do not support routine measurement of Lp(a) for cardiovascular stratification in women."[3]
Stroke, as above	As above	As above	Adjusted HR for ischemic stroke, 1.87; 95% CI, 1.29-2.71	As above	As above
Ariyo et al,[15] 2003; prospective cohort study	5888 Community-dwelling adults >65 y followed up for 7.4 y (median)	Top quintile (8.2-47.5) vs bottom quintile (0.1-1.2); ie, Lp(a) levels varied nearly 500-fold despite use of a single isoform-sensitive assay	Unadjusted risk of vascular death in men: RR, 2.54; 95% CI, 1.59-4.08 Unadjusted risk of all-cause mortality in men: RR, 1.76; 95% CI, 1.31-2.36	Risk relationships were similar after adjusting for conventional CVD risk factors No association was seen between Lp(a) and vascular risk in elderly women	Among older US adults, elevated Lp(a) is an independent predictor of stroke, death from vascular disease, and death from any cause in men but not in women. These data support the use of Lp(a) in predicting the risk of these events in older men

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TABLE 1. Continued

Reference, year	Population	Lp(a)-C level (mg/dL)	CVD risk	Other risk relationships	Comment
von Eckardstein et al,[25] 2001; prospective cohort study	788 Men aged 35-65 initially free of CVD and followed up for 10 y	≥17 <17	CHD: 118/1000 42/1000	In men with Lp(a) ≥20 mg/dL **and:** Absolute CVD risk in upper 2 quintiles: RR, 2.7; 95% CI, 1.3-5.7; $P=.006$ LDL-C ≥160 mg/dL: RR, 2.6; 95% CI, 1.2-5.7; $P=.018$) HDL-C ≤35 mg/dL: RR, 8.3; 95% CI, 2.0-35.5; $P=.001$	Potential multiplier effect: relative risk of CVD with elevated Lp(a) increases in the presence of other CVD risk factors (eg, low levels of HDL-C, hypertension, high absolute CVD risk) "The effect of elevated Lp(a) on coronary risk was modulated by other [conventional CVD risk] factors."[25]
Danesh et al,[27] 2000; meta-analysis of 27 prospective studies with ≥1-y follow-up, 1988-1999	Mostly whites in population-based cohorts. Weighted mean BL age, 51 y. Weighted mean follow-up, 10 y	Upper vs lower tertile	Combined risk ratio, 1.6; 95% CI, 1.4-1.8; $P<.0001$	Not applicable	Not applicable

[a]apo = apolipoprotein; BL = baseline; CHD = coronary heart disease; HDL-C = high-density lipoprotein cholesterol; HR = hazard ratio; LDL-C = low-density lipoprotein cholesterol; MI = myocardial infarction; OR = odds ratio; PY = person-years; RR = relative risk.

[b]SI conversion factors: To convert HDL-C and LDL-C values to mmol/L, multiply by 0.0259; to convert Lp(a) values to μmol/L, multiply by 0.0357.

placebo at treatment year 1, incidences of CV events at year 3 were similar in the 2 treatment groups[40] (Figure 2).

Study limitations may have reduced the capacity to determine associations between changes in Lp(a) and coronary events on active treatment compared with placebo. Most patients in both treatment arms had LDL-C near or at goal (median, 72 mg/dL) on baseline statins, and significantly higher proportions of the control group received ezetimibe or maximum-dose simvastatin (vs the active treatment group). These interventions may have served to "delipidate" or otherwise stabilize plaque in both study arms, minimizing discernible on-treatment differences.

The Heart Protection Study 2-Treatment of HDL to Reduce the Incidence of Vascular Events

The Heart Protection Study 2-Treatment of HDL to Reduce the Incidence of Vascular Events (HPS2-THRIVE)[41] involved over 25,000 individuals with preexisting vascular disease who were initially treated with simvastatin (40 mg) and ezetimibe (if needed). Patients were then randomized to either niacin in combination with laropiprant or to placebo. Laropiprant was added to attenuate niacin-induced, receptor-mediated, prostaglandin-driven vasodilation with subsequent subcutaneous flushing. In the HPS2-THRIVE, treatment with niacin-laropiprant together with statins and/or ezetimibe conferred no cardioprotective benefit compared with background statin-ezetimibe therapy alone in reducing CVD events.

Similar to the findings in the AIM-HIGH trial,[40] in the HPS2-THRIVE there was no incremental benefit of niacin when added to a statin in patients whose LDL-C levels were near or at LDL-C goal at baseline: 63 mg/dL in the HPS2-THRIVE and 72 mg/dL in the AIM-HIGH study.[40,41] However, in the HPS2-THRIVE, laropiprant treatment may have complicated associations between lipid-altering treatment and CVD rates.

OVERVIEW OF CURRENTLY APPROVED TREATMENTS THAT LOWER Lp(a)

Lipid Therapies

Niacin monotherapy and niacin-containing regimens are the only lipid pharmacological

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treatments that consistently, markedly, and dose-dependently lower Lp(a) and have been recognized as such by consensus clinical guideline panels.[42-44] Percent lowering tends to be greater at higher baseline Lp(a) values. In clinical trials, niacin-containing regimens (with minimum daily niacin doses of ≥1.0 g) reduced Lp(a) by approximately 7% to 40%.[45-51] At daily doses of 1.0 g of niacin (among studies in which specific niacin dosing data are available), niacin-containing regimens reduced Lp(a) by approximately 5% to 17%.[45-49,52,55,61]

Niacin therapy likely reduces Lp(a) by decreasing mobilization of free fatty acids from adipose tissues. Reduced trafficking of unesterified fatty acids to the liver may lower Lp(a) by attenuating hepatic synthesis of apo B. Niacin stimulates degradation of apo B–containing lipoproteins and decreases triglyceride synthesis by inhibiting diacylglycerol acyltransferase 2.[62] Possibly because hepatic complexation of apo(a) to apo B_{100} is facilitated by intracellular triglyceride synthesis, niacin-dependent decreases in Lp(a) may be especially marked in patients with hypertriglyceridemia. It is also possible that niacin inhibits hepatocyte linkage of oxidized lipids to apo(a), generating a relatively benign species of apo(a).

Estrogen or Hormone Replacement Therapy

Elevated Lp(a) is associated with increased coronary risk in both premenopausal and postmenopausal women.[32,63] However, as with the case for pharmacologically reducing Lp(a) in order to decrease CV risk in overall populations, the argument as related to postmenopausal women is controversial. A US Preventive Services Task Force recently issued a recommendation against routine use of hormone replacement therapy (HRT) to prevent chronic conditions, including unopposed estrogen to prevent CHD.[64]

Clinical and observational studies in women with or without a history of CHD have shown potential *increases* in the risks of thromboembolic stroke, venous thromboembolism, and cholecystitis among women receiving HRT; these and other studies have largely excluded a role for long-term HRT to prevent chronic diseases, including CHD, in postmenopausal women.[65-68] The Heart and Estrogen/progestin Replacement Study (HERS), a major study of HRT for secondary prevention in postmenopausal women, did not find any decrease in overall CV risk with HRT despite lowering of Lp(a) vs placebo[65] (Figure 2).

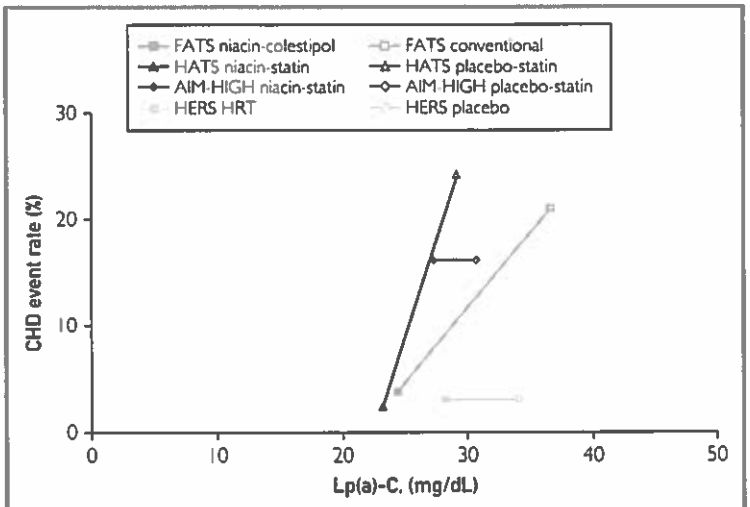

FIGURE 2. Effects of different pharmacotherapies on lipoprotein(a) cholesterol (Lp[a]-C) and the incidence of coronary heart disease (CHD). AIM-HIGH = Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health; FATS = Familial Atherosclerosis Treatment Study; HATS = HDL-Atherosclerosis Treatment Study; HERS = Heart and Estrogen/progestin Replacement Study (high-Lp[a] quartile subgroup); HRT = hormone replacement therapy.

Multivariate adjusted relative hazards of primary CHD events and coronary revascularization in the placebo group tended to be significantly higher among postmenopausal women with greater baseline Lp(a)-C levels (eg, in the fourth quartile [55.0-236.0 mg/dL] compared with the first quartile [0-7.0 mg/dL]; $P \leq .04$ for trends).[69] Women with elevated Lp(a)—either above the median or in higher quartiles of the distribution—derived greater potential cardioprotective effects from HRT than their counterparts with lower Lp(a) values; there was a significant interaction of baseline Lp(a), HRT treatment, and CHD risk.[69]

OTHER NONPHARMACOLOGICAL INTERVENTION: LDL APHERESIS

Low-density lipoprotein apheresis is typically reserved for patients with profoundly elevated lipoprotein levels.[70] Low-density lipoprotein apheresis techniques available in North

America include dextran sulfate cellulose adsorption and heparin-induced extracorporeal LDL-C precipitation. Most LDL apheresis procedures are well tolerated, with maximum 5% incidences of most adverse events (including bradykinin-driven anaphylactoid responses and reductions in HDL-C).[70]

In the Low-Density Lipoprotein Apheresis Angioplasty Restenosis Trial, the rate of restenosis after percutaneous coronary intervention was 21% in 42 patients with at least 50% reductions in Lp(a), compared to 50% among 24 patients with lower percent reductions in Lp(a), using LDL apheresis via dextran sulfate cellulose adsorption ($P<.05$).[71,72] After percutaneous coronary intervention, a restenosis rate of 12.5% was observed after LDL apheresis with adjunctive niacin-pravastatin that reduced Lp(a) by at least 50% compared to 53% with lower percent Lp(a) reductions.

SUGGESTED TREATMENT ALGORITHM

A new clinical algorithm to inform lipid-altering treatment decision making in patients with elevated Lp(a) focuses largely on consensus guidelines and synthesis of findings from recent studies (Figure 3). While noting that niacin can lower Lp(a) by up to 30%, the National Cholesterol Education Program Adult Treatment Panel III stated that it was unclear whether such Lp(a) reductions induced by niacin decrease CHD risk: "the quantitative contribution of elevated Lp(a) to CHD risk beyond the major risk factors is uncertain. This uncertainty extends both to individuals and populations; in the latter, the frequency of elevated Lp(a) is not as high as for the major risk factors."[13]

As mentioned previously, no RCT involving lipid pharmacotherapy has explicitly ascribed reduced CV risk specifically to the lowering of Lp(a) with either niacin or other pharmacotherapies. Given the strong evidence base supporting the cardioprotective benefits of lowering LDL-C with statins, and the multiplier effects on CV risk of elevated Lp(a) when in the presence of increased LDL-C levels, the first lipid treatment target should be to reduce LDL-C. A prospective cohort study at the Cleveland Clinic (a GeneBank study) revealed that the attributable risk of CV events associated with elevated Lp(a) is markedly attenuated in patients with LDL-C levels below 70 mg/dL after aggressive pharmacotherapy.[73]

Lipoprotein(a) screening can also improve discrimination and stratification of CV risk. Such testing should be conducted in patients with elevated LDL-C together with a personal or family history of premature CVD, familial hypercholesterolemia (FH), recurrent cardiovascular events despite maximum statin therapy, or insufficient LDL-C responses to statins (Figure 3). If the Lp(a)-C level is at or above 30 mg/dL (>75th percentile in most population distributions), clinicians should institute maximum-potency statins or statin combinations (with sequestrants or ezetimibe) to decrease LDL-C levels to below 70 mg/dL or achieve a minimum 50% reduction in LDL-C. (However, further LDL-C reductions on treatment with either ezetimibe monotherapy or bile acid resins apart from cholestyramine have not been associated with significant incremental reductions in incidences of CVD.)

If the LDL-C level remains at or above 70 to 100 mg/dL, adding niacin, up to 2 g daily, is a rational approach to further reduce apo B_{100}, which is a component of both LDL-C and Lp(a). Of note, niacin treatment is not recommended if patients are using high-potency statins and their LDL-C levels are already at goal (<70 mg/dL). Confirming the multiplier effect of elevated Lp(a) in the presence of elevated LDL-C were findings from the recent large angiographic study from the GeneBank program.[73] Baseline Lp(a)-C levels of 30 mg/dL or above were significantly associated with 3-vessel/obstructive disease or major adverse coronary events (death, myocardial infarction, stroke, revascularization) in patients with LDL-C levels ranging from 70 to 100 mg/dL ($P=.049$) and above 100 mg/dL ($P=.02$) but not below 70 mg/dL ($P=.77$).

In addition, in a recent subgroup analysis of the AIM-HIGH trial, baseline and on-treatment levels of Lp(a) significantly predicted CV events in each treatment group; however, extended-release niacin treatment reduced Lp(a) by 21% but did not significantly affect CV risk.[74] Data from a larger subgroup analysis of the HPS2-THRIVE in patients with different levels of Lp(a) are eagerly awaited.

A recent systematic review and meta-regression analysis of 11 RCTs including nearly 10,000 patients revealed that niacin treatment was associated with a significant decline in any

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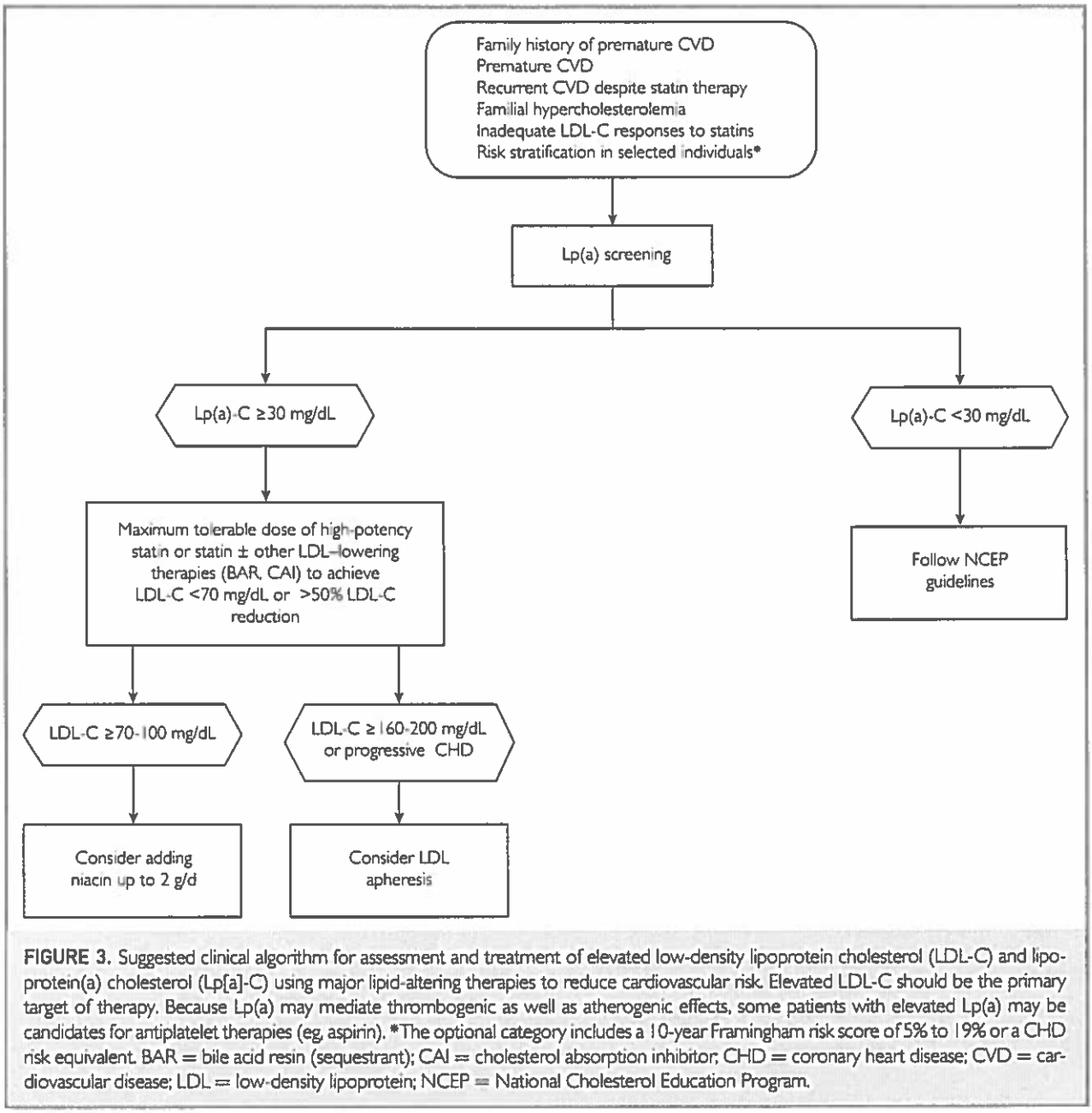

FIGURE 3. Suggested clinical algorithm for assessment and treatment of elevated low-density lipoprotein cholesterol (LDL-C) and lipoprotein(a) cholesterol (Lp[a]-C) using major lipid-altering therapies to reduce cardiovascular risk. Elevated LDL-C should be the primary target of therapy. Because Lp(a) may mediate thrombogenic as well as atherogenic effects, some patients with elevated Lp(a) may be candidates for antiplatelet therapies (eg, aspirin). *The optional category includes a 10-year Framingham risk score of 5% to 19% or a CHD risk equivalent. BAR = bile acid resin (sequestrant); CAI = cholesterol absorption inhibitor; CHD = coronary heart disease; CVD = cardiovascular disease; LDL = low-density lipoprotein; NCEP = National Cholesterol Education Program.

CHD (P=.02) or any CVD (P=.007) event.[75] However, the analysis included the AIM-HIGH study but not the HPS2-THRIVE. Subgroup analyses, potentially including patient segments with elevated Lp(a), may show incremental benefits of niacin when administered in combination regimens.[76] The Lp(a)-lowering effects of niacin must be weighed against potential adverse effects, many of which are time-limited/reversible in individual patients: flushing, gastrointestinal disorders (eg, peptic ulcer), reduced insulin sensitivity, increased uric acid, and atrial fibrillation.

Returning to the algorithm, if the LDL-C level remains at 160 to 200 mg/dL or higher, or the patient has progressive CHD on maximal therapy, LDL apheresis should be considered. However, this use of LDL apheresis and its use to specifically lower Lp(a) have not been approved by the US Food and Drug Administration and are hence considered

off-label. A repeated Lp(a) measurement is generally not recommended in consensus guidelines but may be useful in evaluating responses to therapy.

A position statement by the National Lipid Association for patients with FH recommended that physicians consider LDL apheresis for patients using maximal drug therapy (1) whose LDL-C level is at least 200 mg/dL in the presence of 2 risk factors or a high Lp(a)-C level (≥50 mg/dL) and (2) who have LDL-C levels at or above 160 mg/dL and very high-risk characteristics, including established CHD, other CVD, or diabetes.[77] At this writing, LDL apheresis is not a widely available treatment.

The clinical algorithm identifies an Lp(a)-C level above 30 mg/dL as a threshold to institute high-potency statins to reduce LDL-C levels to below 70 mg/dL (or to attain at least a 50% LDL-C reduction) in order to minimize CVD risk. If high-intensity statin therapy is inadequate to achieve this goal, then other evidence-based LDL–lowering therapies should be considered in combination with statins. If LDL-C values remain above 70 to 100 mg/dL despite high-intensity statin therapy with or without other LDL–lowering therapies, then niacin therapy should be contemplated as a further means to reduce all apo B–containing lipoproteins, including LDL and Lp(a). The algorithm thus represents a stepped-care approach to minimize the residual risk conferred by an elevated Lp(a) level. The role of Lp(a) screening is not specifically part of a strategy to reduce CVD risk by lowering Lp(a) but rather a way to identify patients who warrant more aggressive overall lipid-lowering therapy to reduce all apo B–containing lipoproteins.

According to the European Atherosclerosis Society, Lp(a)-C should be lowered to below the 80th percentile, or less than 50 mg/dL, using niacin in patients with the characteristics noted previously, including FH and recurrent CVD[42] (Figure 3). However, desirable Lp(a)-C levels may be closer to below 30 or 40 mg/dL. When the Lp(a)-C level is above 30 mg/dL and the Lp(a) particle (Lp [a]-P) level is above 72 nmol/L (mean conversion factor of 2.4:1[78]), the patient should be considered at elevated atherosclerotic and thrombogenic risk and may be a candidate for antiplatelet (aspirin), as well as lipid-altering, therapy. (See the "Lp(a) Measurement Issues" section for further information about assaying different Lp[a] subfractions.)

In a meta-analysis, a US Preventive Services Task Force panel also identified an Lp(a)-C level of 30 mg/dL as a potential decision limit, noting that the relative risk of CHD increased by nearly 60% in those with levels above (vs below) this threshold.[79,80] Some clinical laboratories use 30 mg/dL as a cut point to define elevated Lp(a)-C. A single Lp(a)-C measure below 25 mg/dL largely rules out elevated Lp(a) as a contributor to advanced CV risk in an individual. Recent guidelines from the Canadian Cardiovascular Society also noted that Lp(a)-C levels above 30 mg/dL are associated with increased CV risk.[81]

Recently reported data from the Copenhagen City Heart Study (CCHS) indicated that the presence of extremely elevated Lp(a)-C—above the 80th percentile (>47 mg/dL)—significantly enhanced prediction of coronary events compared with existing conventional CHD risk factors alone.[82] As shown in the algorithm, Lp(a) can be measured in order to further stratify selected individuals with intermediate-risk profiles, including a 10-year Framingham risk score of 5% to 19% or a CHD risk equivalent. Given the findings from the CCHS, it is plausible that the presence of an Lp(a)-C level above the 80th percentile (>50 mg/dL) could move such an intermediate-risk patient into the secondary prevention category, warranting more aggressive apo B–lowering therapy via statins and/or niacin. The CCHS data could also potentially support the use of a higher Lp(a)-C cut point (ie, >80th percentile; ≥50 mg/dL) to predict CHD and inform clinical decisions.

LPA genotyping may assist in determining the presence of allelic gene variants (eg, rs3798220, rs10455872, rs9457951, rs41272110) that may be associated with increased Lp(a) levels and/or elevated CV risk. The presence of these SNPs could, in theory, signal a potential benefit from more intensive treatment of Lp(a) and LDL-C, either to lower levels or to higher absolute decreases (mg/dL) from baseline. Patients with these gene variants (including carriers) may also benefit from addition of aspirin or other antiplatelet therapies to reduce coronary events; a precedent for this strategy was established in both the Women's Health Study and the Atherosclerosis in Communities

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(ARIC) trial. In these studies, carriers of the rs3798220 allele experienced a significant decrease in coronary events while receiving aspirin therapy, whereas noncarriers did not.[83-86]

In summary, the clinical algorithm presented in this article is consistent with the National Cholesterol Education Program Adult Treatment Panel III view that measuring Lp(a) is an option that may help to further risk stratify patients with a "strong family history of premature CHD or...with...familial hypercholesterolemia."[43] Among such patients, "an elevated Lp(a)...presents the option to raise a person's risk to a higher level...The finding of a high Lp(a) could count as a second risk factor"[43] to warrant treatment of LDL-C to a lower target.

Lp(a) MEASUREMENT ISSUES

For decades, issues surrounding Lp(a) measurement and standardization have complicated interpretations of Lp(a) levels in the context of CVD risk. In addition, most clinical laboratories have used various methods of reporting Lp(a) levels that have been confusing to clinicians. Some clinical laboratories are still reporting Lp(a) mass, whereas others report Lp(a)-C, Lp(a) protein, or Lp(a)-P. This variability has created confusion for clinicians who are not knowledgeable about how clinical laboratories measure and report Lp(a) values. Over the years, several efforts have been undertaken to enhance standardization of the measurement and reporting of Lp(a) levels.

A National Heart, Lung, and Blood Institute panel advocated expression of Lp(a) levels in nmol/L of protein, in order to capture the total number of Lp(a)-Ps (by analogy to apo B signifying the total number of atherogenic lipoprotein particles). According to the National Heart, Lung, and Blood Institute, Lp(a) levels above the 75th percentile are associated with increased CV risk; in whites (in the Framingham Heart Study), this percentile translates to above 75 nmol/L of Lp(a) protein.[44] If an apo(a) isoform–sensitive assay is used, Lp(a) protein values above 50 nmol/L should be retested, according to validated methods, by a referral laboratory.

Most available assays to evaluate Lp(a) levels include an immune/antibody component (eg, immunonephelometry, immunoturbidimetry, latex immunoassays). The recent European Atherosclerosis Society guidelines recommended the use of assays with coefficients of variation below 10% that are also economically priced and accurate.[42]

Immunoassays, other methods of quantifying Lp(a) (eg, vertical auto profile, β-lipoprotein cholesterol quantitation with polycations[87-89]), and protocols for phlebotomy and plasma storage should be standardized for quality control, including the use of an Lp(a) preparation approved as a secondary reference by international agencies (World Health Organization, International Federation of Clinical Chemistry). The current International Federation of Clinical Chemistry reference material, with an assigned value of 107 nmol/L for Lp(a) protein, should be used to calibrate assays. Manufacturers of assays for Lp(a) should seek to minimize the effects of apo(a) size on Lp(a) levels.[90]

An early assay (Northwest Lipid Research Laboratories) with accuracy not influenced by the heterogeneity of apo(a) isoform size utilized a monoclonal antibody targeted against a unique apo(a) epitope (within KIV-9 and not within the variable part of the protein sequence); the monoclonal antibody was then used to generate an enzyme-linked immunosorbent assay. This assay specifically and size-independently measures Lp(a)-P number in SI units (mol/L or similar units such as nmol/L).[91]

Total Lp(a) mass can also be measured. One validated, high-quality assay is the Denka-Seiken immunoturbidimetric assay (Atherotech Diagnostics Lab; Berkeley Extended-Range Lp[a] Test). Results are expressed in mg/dL, and the coefficient of variation is less than 3%. Lipoprotein(a)-C can be measured with density-gradient tests such as vertical auto profile or β-lipoprotein cholesterol quantitation with polycations.[88,89] A lipoprotein quantitative immunofixation electrophoresis assay developed by Health Diagnostic Laboratory, Inc measured Lp(a)-P number in a manner that correlated strongly with a research methodology but not with the Denka-Seiken Lp(a) mass assay, most likely because the mass assay is sensitive to size variations in apo(a) isoforms. Electrophoresis is highly specific (~93%) but not sensitive (60%) for Lp(a) mass exceeding 30 mg/dL.[92]

One way to help discriminate CV risk associated with elevated Lp(a) is to obtain measures of both Lp(a)-P and Lp(a)-C. Evidence suggests that Lp(a)-P and Lp(a)-C are complementary subfractions in terms of conferring CV risk. In one study, the ratio of Lp(a)-C to Lp(a)-P was 0.46 in healthy individuals, 1.40 in those with Lp(a)-C above the upper limit of normal (10 mg/dL), 0.06 in those with Lp(a)-P above the upper limit of normal (70 nmol/L), and 0.08 in those with elevations in both fractions.[93]

Assays of Lp(a) fractions were developed by Joseph P. McConnell, PhD, of the Mayo Clinic and Mayo Foundation for Medical Education and Research. Two patients may have identical levels of Lp(a) mass, but in the patient with smaller Lp(a) containing lower-molecular-weight apo(a) isoforms (the liver secretes smaller apo[a] particles more readily than larger ones), greater amounts of cholesterol are trafficked by Lp(a), and hence Lp(a) elevations may be potentially more atherosclerotic and thrombogenic. The patient with an Lp(a)-C level of at least 30 mg/dL (75th percentile population risk cut point) and elevated Lp(a) mass may be at particularly elevated CV risk. On the other hand, in the presence of predominantly large apo(a) isoforms, an Lp(a)-C level of 30 mg/dL places a patient at only the 50th percentile of CV risk. Protocols for quantification of different apo(a) isoforms (including heterogeneous kringle architectures) have been developed by Drs Marlys Koschinsky and Santica Marcovina.[88,90] However, the relative prognostic utility of assaying Lp(a) by particle number (Lp[a]-P), cholesterol (Lp[a]-C), or mass remains controversial at this writing. In one clinical trial reported by McConnell et al,[94] Lp(a)-C was an independent predictor of angiographic CHD and CVD events, whereas Lp(a) mass was not an independent risk factor for these outcomes.

THE WAY FORWARD

To inform controversies surrounding Lp(a), prospective RCTs are being conducted to determine whether pharmacotherapies that lower Lp(a) also decrease CV risk[95-103] (Table 2). As mentioned previously, the HPS2-THRIVE reported that treatment with niacin-laropiprant together with statins and/or ezetimibe conferred no cardioprotective benefit compared with background statin-ezetimibe therapy alone in reducing CV events.[41] However, it is possible that patients with elevated Lp(a) at baseline experienced special benefits of the combination niacin regimen, but the number of such individuals may be insufficient to draw statistically valid conclusions. Published results of this clinical trial are eagerly awaited. Trials evaluating investigational agents that also lower Lp(a) (Table 2) may be useful in future efforts to determine the role of on-treatment changes in Lp(a) compared with other lipids in preventing CVD.

CONCLUSION

Lipoprotein(a) is a genetic, causal risk factor for CVD. Population-based studies have determined that there is a continuous, graded association between Lp(a) levels and CV risk that is somewhat less marked compared with the association of elevated LDL-C and such risk. Partly because both Lp(a) and LDL-C contain the atherogenic moiety apo B_{100}, there is a multiplier effect such that CV risk is synergistically increased when both lipoproteins are elevated; conversely, elevated Lp(a) becomes more clinically innocuous when accompanied by lower levels of LDL-C (<70 mg/dL after maximum statins). Elevated LDL-C (or apo B) should always be targeted for lipid-modifying therapy before treating elevated Lp(a).

Niacin reduces Lp(a) by up to 40% and has been identified by consensus treatment panels as the only medication that consistently lowers Lp(a). Because niacin treatment can reduce the apo B_{100} component of both LDL and Lp(a), such therapy is a rational alternative in the presence of refractorily elevated LDL-C despite maximum-dose statins or statin combination therapy. Further clinical trials are needed to determine if reductions in CV risk can be specifically ascribed to on-treatment changes in Lp(a).

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TABLE 2. Ongoing Clinical Trials With Niacin and Other Investigational Agents That Lower Lipoprotein(a)[a,b]

Agent; study (clinicaltrials.gov identifier)	Study setting/design (status)	Patients	Treatments	Main outcome measures	Comment
Approved					
Niacin regimens; NICOLa (NCT00633698)	German phase 3 RCT (recruitment status unknown)	Lp(a)-C >30 mg/dL, TG <400 mg/dL with or without CVD	ERN 0.5-2.0 g + ongoing statin vs Pbo + ongoing statin (at stable doses) for 20 wk	Primary: Percent change in Lp(a) Secondary: Percent change in LDL-C, HDL-C, TG, blood glucose	Other: adverse clinical events, HR-QOL, disease-related costs
Niacin regimens; Effect of Niacin in the Lipoprotein(a) Concentration (NCT01321034)	Spanish phase 4 open-label trial (completed)	LDL-C 70-190 mg/dL + Lp(a) <30 ("normal"), 30-60 ("high"), or >60 ("very high") mg/dL	ERN/LRPT 1-2 g/20-40 mg for 12 wk	Primary: Absolute and relative change in Lp(a) stratified by BL Lp(a) Secondary: Percent change in Lp(a) stratified by number of KIV-2 repeats in apo(a) gene	None
Investigational					
ASO (MPMN [ISIS 301012]); FOCUS FH[95,96] (NCT01475825)	North American phase 3 RCT (recruiting)	Severe HeFH (LDL-C ≥200 mg/dL [with CHD] or ≥300 mg/dL)	Weekly SC: MPMN 200 mg 1×/wk or MPMN 70 mg 3×/wk vs Pbo for each (each for 60 wk)	Primary: Percent change in LDL-C Secondary: Percent change in Lp(a)	Other: Percent change in apo B Frequencies of adverse events and injection-site reactions
CETP inhibitor (ANA); REVEAL[97-102] (NCT01252953)	International (Europe, UK, Scandinavia, Asia, North America) Phase 3 RCT (recruiting)	≥50 y + MI history, CBVD, PVD, or DM + symptomatic CHD	ANA 100 mg/d (or Pbo) + statins for 4 y	Primary: Major coronary events (coronary death, MI, coronary revascularization)	Other: Percent change in lipids/ lipoproteins
PCSK9 mAb (REGN727/ SAR236553); ODYSSEY FH I[103] (NCT01623115)	US and South African phase 3 RCT (recruiting)	HeFH not adequately controlled on LMT: LDL-C ≥70 mg/dL with CVD or LDL-C ≥100 mg/dL without CVD	PCSK9 mAb (vs Pbo) SC + ongoing LMT for up to 24-88 wk	Primary: Percent change in LDL-C up to 24 wk Secondary: Percent change in other lipids/lipoproteins up to 78 wk	None
PCSK9 mAb (REGN727/ SAR236553); ODYSSEY Outcomes[103] (NCT01663402)	US phase 3 RCT (recruiting)	≥40 y + hospitalized for acute coronary syndrome within prior 16 wk	PCSK9 mAb (vs Pbo) SC + ongoing LMT for up to 280 wk	Primary: Time to first major CVD event	Other: Percent change in lipids/ lipoproteins

[a]ANA = anacetrapib; apo = apolipoprotein; ASO = antisense oligonucleotide; BL = baseline; CBVD = cerebrovascular disease; CETP = cholesteryl ester transfer protein; CHD = coronary heart disease; CVD = cardiovascular disease; DM = diabetes mellitus; ERN = extended-release niacin; FOCUS FH = Study of the Safety and Efficacy of Two Different Regimens of Mipomersen in Patients With Familial Hypercholesterolemia and Inadequately Controlled Low-Density Lipoprotein Cholesterol; HDL-C = high-density lipoprotein cholesterol; HeFH = heterozygous familial hypercholesterolemia; HR-QOL = health-related quality of life; KIV-2 = kringle IV type 2; LDL-C = low-density lipoprotein cholesterol; LMT = lipid-modifying (drug) therapy; Lp(a) = lipoprotein(a); LRPT = laropiprant; mAb = human monoclonal antibody; MI = myocardial infarction; MPMN = mipomersen; NICOLa = Evaluation of the Effect of NICOtinic Acid (Niacin) on Elevated Lipoprotein(a) Levels; ODYSSEY FH I = Efficacy and Safety of Alirocumab SAR236553 (REGN727) Versus Placebo on Top of Lipid-Modifying Therapy in Patients With Heterozygous Familial Hypercholesterolemia Not Adequately Controlled With Their Lipid-Modifying Therapy; ODYSSEY Outcomes = Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab SAR236553 (REGN727); Pbo = placebo; PCSK9 = proprotein convertase subtilisin/kexin type 9; PVD = peripheral vascular disease; RCT = randomized placebo-controlled trial; REVEAL = Randomized EValuation of the Effects of Anacetrapib Through Lipid-modification; SC = subcutaneous; TG = triglycerides.

[b]SI conversion factors: To convert Lp(a) values to μmol/L, multiply by 0.0357; to convert triglyceride values to mmol/L, multiple by 1.8; to convert LDL-C values to mmol/L, multiply by 0.0259.

Abbreviations and Acronyms: **AIM-HIGH** = Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health Outcomes; **apo** = apolipoprotein; **CCHS** = Copenhagen City Heart Study; **CHD** = coronary heart disease; **CV** = cardiovascular; **CVD** = CV disease; **FH** = familial hypercholesterolemia; **HDL-C** = high-density lipoprotein cholesterol; **HPS2-THRIVE** = Heart Protection Study 2-Treatment of HDL to Reduce the Incidence of Vascular Events; **HRT** = hormone replacement therapy; **KIV-2** = kringle IV type 2; **LDL** = low-density lipoprotein; **LDL-C** = LDL cholesterol; **Lp(a)** = lipoprotein(a); **Lp(a)-C** = Lp(a) cholesterol; **Lp(a)-P** = Lp(a) particle; **PN** = pentanucleotide; **RCT** = randomized controlled trial; **SNP** = single-nucleotide polymorphism

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