Elevated Lipoprotein A in South Asians and the Associated Risk of Cardiovascular Disease: A Systematic Review

Subrata Kar, DO, FACC, FSCAI

Abstract: *Background*: South Asians have a premature risk of cardiovascular disease and increased lipoprotein A which enhances their risk. *Methods*: This systematic review evaluates the role of elevated lipoprotein A in cardiovascular disease risk for South Asians. It discusses the pathophysiology, clinical studies, and treatment of elevated lipoprotein A using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses method. *Results*: A total of 72 articles was incorporated which consisted of clinical studies, case-control and cohort studies, meta-analysis, reviews, and editorials. Cardiovascular disease and myocardial infarction occurs prematurely in South Asians, which is further enhanced with an elevated lipoprotein A. *Conclusions*: South Asians with an elevated lipoprotein A have an increased risk of coronary artery disease so they should have early enactment of lifestyle modification and aggressive medical management. (Curr Probl Cardiol 2021;46:100581.)

Introduction

South Asia consists of India, Pakistan, Afghanistan, Nepal, Bangladesh, and Sri Lanka.[1] It comprises 24% of the world's population being the most densely populated geographical region (1.891 billion).[2] South Asians (SA) have an increased risk of cardiovascular disease (CVD).[3-7] It starts 5-10 years earlier than other ethnicities.[7-9] SA

Declaration of competing interest: The authors have no conflicts of interest to disclose.

Curr Probl Cardiol 2021;46:100581
0146-2806/$ – see front matter
https://doi.org/10.1016/j.cpcardiol.2020.100581

have higher lipoprotein A [(Lp(a)] levels which is associated with an increased risk of myocardial infarction (MI) and CVD. In this systematic review, the importance of SA ancestry with elevated Lp(a) and CVD is discussed. The understanding of amplified CVD risk in SA by internists, cardiologists, cardiac surgeons, and interventional cardiologists will improve their treatment. This review will augment the reader's knowledge about SA CAD risk so early implementation of lifestyle modification and optimal medical therapy can be initiated.

Methods

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) method was utilized to obtain relevant articles for the systematic review (Fig 1). An extensive PubMed, PubMed Central, National Library of Medicine, and Medline search was performed in October 2019 using the words, "Lp(a) and coronary artery disease (CAD) in SA", "Lp(a) and CAD", and "Lp(a) and SA".

A total of 2775 articles was found, of which, 2723 involved CAD and Lp(a), SA with CAD, and/or Lp(a) in SA. Articles were excluded if they were duplicates, case reports, abstracts, and/or unrelated to the search criteria. No date restrictions were applied for article exclusion. Clinical trials, observational studies, meta-analyses, reviews, and editorials were included. Only studies performed in adults and published in English were included (n = 72).

Results

Structural Composition and Basic Genetics of Lp(a)

Lp(a) is a low-density lipoproteins (LDL) like particle with oxidized phospholipids which are attached to apolipoprotein B-100 and apolipoprotein A (Apo A) via a single covalent disulfide bond.[3,10,11] The Apo A contains 10 different subtypes of KIV protease domain repeats (derived from kringle IV).[12] KIV_2 may be present in various copies of 1 to >40 creating >40 isoforms and >40 dissimilar sized Lp(a) particles.[3,13-15] Such isoforms are inherited from each parent (>80% carry 2 different isoforms). Larger allele-specific Apo A isoforms with a greater number of KIV repeats induces a lower Lp(a) level, while smaller Apo A allele isoforms with less KIV repeats corresponds to a higher Lp(a) level and increased risk of MI.[16-18] Apo A originated and evolved from the plasminogen gene (synthesized predominantly in the liver), so it can compete

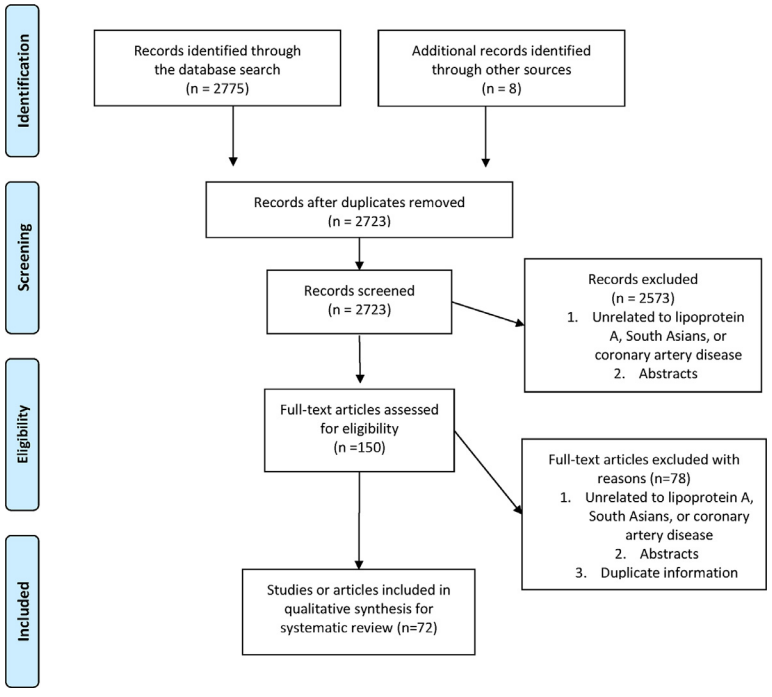

FIG 1. Articles for lipoprotein A, South Asians, and coronary artery disease using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) method. (Color version of figure is available online.)

with plasminogen binding, thereby, inhibiting plasminogen activation inducing a prothrombotic state.

The Lp(a) gene locus primarily determines Lp(a) levels (>90% genetically determined), which is not substantially affected by environmental or dietary modifications. Three chromosomal regions (6q26-27, 9p21, and 1p13) are associated with increased CAD risk (Copenhagen City Heart Study).[19] The Lp(a) locus on 6q26-27 had the greatest association with common variants (rs10455872 and rs3798220) displaying an odds ratio (OR) for CAD of 1.70 (95% confidence interval [CI], 1.49 to 1.95) and 1.92 (95% CI, 1.48 to 2.49).[19] Figure 2 displays the structure and composition of Lp(a).

Pathophysiology and Significance of Elevated Lp(a)

Lp(a) levels are genetically predetermined and remain fairly constant throughout life.[20] Lp(a) levels above 50 milligrams/deciliter (mg/dL) or

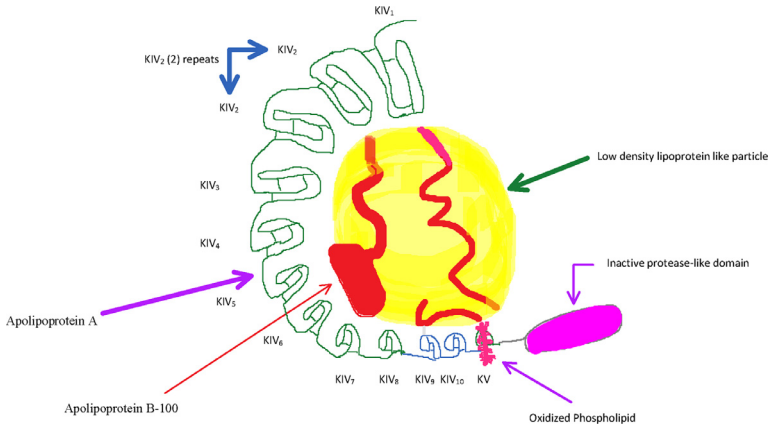

FIG 2. Structure of Lipoprotein A consisting of Apolipoprotein B-100, oxidized phospholipid, low density lipoprotein like particle, and Apolipoprotein A. (Color version of figure is available online.)

125 nanomoles/liter are considered high. Elevated Lp(a) is an independent risk factor for premature CAD.[21-26] Lp(a) has been causally associated with the risk for MI and CAD.[17,26-28] Moreover, oxidized Lp(a) has also been associated with the presence and severity of acute coronary syndrome (ACS).[29] Lp(a) inhibits transforming growth factor beta and it increases monocyte adhesion and migration.[11,30] It promotes the recruitment of inflammatory cells to the endothelium and augments migration and proliferation of smooth muscle cells.[11,30] Lp(a) induces a proinflammatory, prothrombotic, and proatherogenic state via oxidized phospholipids contained in Apo A.[13,31] Therefore, it increase the risk of MI and stroke based on epidemiological studies and meta-analyses.[17,18,32]

In a Danish general population prospective study (Copenhagen City Heart Study) of 8720 patients, extreme Lp(a) levels (≥80th percentile, ≥47 mg/dL) improved the risk prediction of MI and CAD.[33] In a German cohort study (594 males, 40-60 years of age) by Armstrong et al,[34] increased Lp(a) was associated with CAD (≥50% stenosis of ≥1 major epicardial arteries).[34]

A study (1995-1996) of 129 Caucasian patients with chronic stable angina showed that elevated Lp(a) was present in severe CAD (≥70 stenosis on angiography, $P = 0.002$).[35] It was also an independent risk factor for angiographically determined CAD (adjusted OR 9.1, 95% CI 2.0 to 42.1, $P = 0.006$).[35] Nordestgaard et al,[36] advised screening for Lp(a) in intermediate to high risk patients with premature CAD, familial hypercholesterolemia, family history of premature CAD and/or elevated Lp(a),

recurrent CAD despite statin treatment, or ≥10% 10-year risk of fatal and nonfatal MI according to the United States guidelines.

The GeneBank Study[37] of 2769 patients (3-year follow-up) showed that an elevated Lp(a) (≥30 mg/dL, 38%) was associated with a 2.3 fold (95% CI, 1.7 to 3.2, $P < 0.001$) enhanced likelihood of angiographic CAD >50% and a 1.5 fold increased risk of triple vessel CAD (95% CI, 1.3 to 1.7, $P < 0.001$). Elevated Lp(a) increased major adverse cardiovascular events (MACE: 41.8% vs 35.8%, $P = 0.005$; death, MI, stroke, and coronary revascularization). In patients with LDL ≥70-100 mg/dL ($P = 0.049$) and >100 mg/dL ($P = 0.02$), elevated Lp(a) was associated with worse cardiovascular outcomes such as significant obstructive CAD, triple vessel disease, and MACE. However, LDL<70 mg/dL with an elevated Lp(a) showed no adverse outcomes ($P = 0.77$). Thus, elevated Lp (a) and high LDL may predict the need for revascularization and poor cardiovascular outcomes.

Moreover, a cross-sectional study[38] (918 CAD; 829 non-CAD patients) showed that elevated LP(A) was associated with increased CVD in men and women (OR 1.9, CI 1.3 to 2.9). Substantial CVD risk occurred in both genders with Lp(a) >45 mg/dL (OR: 3.7, 95% CI 2.0 to 6.8 in men ≤55; OR: 3.3, 95% CI 1.6 to 6.6 in older women>55). Men>55 did not show increased CVD risk, which may be secondary to survivor bias.

Even after statin treatment for percutaneous coronary intervention (PCI), elevated Lp(a) is associated with worse long-term outcomes from cardiac death and nonfatal ACS.[39] Furthermore, elevated Lp(a) is associated with greater long-term mortality after coronary angiography or PCI (5.8% vs 2.5%, $P = 0.003$) and an independent risk factor for long-term mortality (hazard ratio [HR]: 1.96, 95% CI: 1.07 to 3.59, $P = 0.029$).[40]

The LipidCardio study[41] (n = 1005) showed that patients with elevated Lp(a) (highest quintile) had significantly increased odds of obstructive CAD ($P = 0.005$). In addition, a meta-analysis[42] of 283,328 CAD patients (17 studies) showed that elevated Lp(a) was independently associated with an increased risk of cardiac death and ACS (relative risk 1.78, 95% CI 1.31 to 2.42) along with stroke, coronary revascularization, or death (relative risk 1.29, 95% CI 1.17 to 1.42). In an observational single center study of 6252 patients (follow-up of 3.1 ± 2.2 years), elevated Lp(a) was a predictor of cardiac death and nonfatal MI (HR 1.773, 95% CI 1.194 to 2.634, $P = 0.005$).[43] It was also associated with increased incidence of obstructive CAD (67.1% vs 60.9%, $P < 0.0001$) and 3-vessel obstructive CAD (25.2% vs 17.9%, $P < 0.0001$). Consequently, several studies support the causal relationship of elevated Lp(a) with an amplified risk of

CAD or MI. Nevertheless, most of these studies have been conducted in Caucasians who have different risk factors and characteristics from SA.

Risk of CAD in SA with Elevated Lp(a)

SA have a genetic predisposition for elevated Lp(a).[21] SA have a greater prevalence of diabetes, metabolic syndrome, central obesity, diminished levels of physical activity, hyperlipidemia (high triglycerides and LDL with low high-density lipoprotein [HDL]), insulin resistance, increased thrombosis risk with higher levels of plasminogen activator inhibitor-1, and lower levels of tissue plasminogen activator.[2,44,45] Thus, SA have increased CAD risk factors including hypertension, smoking, diabetes, central abdominal obesity, low fruit and vegetable consumption, and low levels of exercise.[46] Consequently, SA (migrant or native) have an augmented risk for premature CAD and MI.[21]

Asian Indians comprise the majority of SA.[25] India has approximately 31.8 million people with CAD, which is the highest cause of mortality (28%).[25,47] SA have the second highest Lp(a) levels and they have the greatest risk of acute MI from elevated Lp(a).[28] In 1998, the prevalence of CAD in the urban Indian population was 10.5%.[48] The median age of the first MI was 53 years and they had the greatest number of CVD deaths in 2002 (1,531,534 people).[48] Approximately 5%-10% of MIs occur in Indian men and women younger than 40 years.[48]

Enas et al,[28] lists 3 types of CAD patterns in Indians—extreme prematurity, extreme severity, and high mortality at an early age. Despite lower LDL levels in SA, they may have CAD due to an increased atherogenic burden (greater Apolipoprotein B [Apo B] and LDL particle size).[1] SA may also have less cardiac protection from high HDL, possibly due to dysfunctional HDL with small HDL particle size.[1] In a single center retrospective case-controlled study (New Delhi) of ACS patients ($n = 292$, age ≤ 40 years), the most commonly associated risk factors were hyperlipidemia, smoking, low HDL, central obesity, family history of premature CAD, and premature greying of hair.[49] In the presence of high LDL or total cholesterol/HDL ratio, the effects of elevated Lp(a) were worsened. Consequently, SA have risk for premature CAD and MI, which necessitates aggressive prevention and treatment.

Clinical Studies of CAD in SA

Different ethnicities have diverse Lp(a) levels.[50] The INTERHEART study[51] (case-control), evaluated 6086 patients with an initial MI and

6857 controls from 7 ethnicities. Higher Lp(a) levels were associated with an increased risk of MI, which was more prevalent in SA (third highest Lp(a) levels; 18.9 [3.2-88.2]). Caucasians had the second lowest median Lp(a) levels (11.5 [2.0-99.1]). Nine risk factors were associated with 90% of the population attributable risk of acute MI in men and 94% in women consisting of abnormal lipids, smoking, hypertension, diabetes, sedentary lifestyle, high waist-hip ratio, psychological stress, and low consumption of fruits and vegetables.[46] SA had MI at a mean age of 52 compared with 62 (Europeans) and 63 (Chinese).[8]

The Lessons from the London Life Sciences Population Study (LOLIPOPS)[52] of 16,744 SA and 7032 Caucasians (prospective cohort study) showed an enhanced incidence of CAD in SA compared with Caucasians (OR: 2.55, 95% CI 2.26 to 2.87, $P < 0.001$). A twofold greater occurrence of CAD in SA was found across all ages. The Indian Atherosclerosis Research Study[53] of 2305 patients showed that Lp(a), triglycerides, and interleukin-6 were significantly greater in CAD patients. Also, Lp(a) had 83% heritability and SA had greater Lp(a) levels compared with Caucasians.[1] Thus, SA have early CAD and higher Lp(a) levels compared with Caucasians, so data from Caucasians cannot be extrapolated to SA.

In a prospective Canadian cross-sectional study of 985 patients (Europeans, Indians, and Chinese), the Study of Health Assessment and Risk in Ethnic Groups (SHARE)[3] showed that SA had greater levels of Lp(a), homocysteine, fibrinogen, and plasminogen activator inhibitor-1 along with increased total cholesterol, LDL, and triglycerides with lower HDL. SA ethnicity was an independent determinant of cardiovascular events compared with Europeans (odds ratio 4.51, 95% CI 1.46 to 13.89, $P = 0.02$). Hence, SA have heightened thrombogenic and lipid parameters compared with Caucasians.

The Acute Myocardial Infarction in very young adults: India-AMIYA Study[54] (single center prospective) evaluated 1116 consecutive ST elevation myocardial infarction (STEMI) patients (age $\leq$ 30, mean 26.3$\pm$2.9) from March 2013 to February 2015 in Uttar Pradesh, India. STEMI occurred more often in men (n = 1061, 95.1%) with risk factors of smoking (n = 877, 78.5%), family history of premature CAD (n = 522, 46.8%), obesity (n = 437, 39.1%), physical inactivity (n = 432, 38.7%), stressful life events (n = 330, 29.6%), hyperlipidemia (n = 236, 21.2%), hypertension (n = 229, 20.5%), and hyperhomocysteinemia (n = 214, 19.2%).

A case-control study of 200 Indians (CAD, n = 151; healthy controls, n = 49) showed that Lp(a) was associated with clinical and angiographic CAD.[55] Elevated Lp(a) (> 25 mg/dL) was observed in patients with single and triple vessel CAD compared with normal coronaries ($P < 0.05$).

Also, significantly higher Lp(a) was found between single, double, or triple vessel CAD ($P < 0.01$) and Lp(a) positively correlated with vessel lesion severity ($P < 0.005$).[55]

In a prospective cross-sectional case-control study[56] of 300 patients (150 with single, double, and triple vessel CAD; 150 controls) from North India, higher Lp(a) levels were associated with ACS (55.8%) compared with chronic stable angina (35.4 mg/dL vs 23.0 mg/dL, $P < 0.001$). Patients with double and triple vessel CAD had greater Lp(a) levels compared with controls (30.0, 39.05; 20 mg/dL; $P < 0.008$). Lp(a) levels > 40 mg/dL was an independent risk factor for CAD ($P < 0.001$).

In a North Indian study[57] of 380 young patients (n = 220 with angiographic CAD, age<40; 160 healthy controls), Lp(a) levels were higher in CAD patients compared with controls (30 mg/dL vs 12.7 mg/dL, $P < 0.05$) and were independently associated with angiographically documented CAD. In another North Indian cross sectional study[58] of 360 patients, Lp(a) levels were greater in CAD compared with the non-CAD group (48.7 ± 23.8 mg/dL vs 18.9 ± 11.1 mg/dL, $P < 0.0001$). Elevated Lp(a) showed a causal independent risk for CAD. The Singapore Cardiovascular Cohort Study[5] showed that SA had three times the risk of CAD compared with Chinese (overall-adjusted HR 3.1, 95% CI 2.0 to 4.8). Therefore, several studies of SA with elevated Lp(a) show the worsened risk of CVD, MI, and CAD severity along with a genetic predisposition for premature CAD. Consequently, prevention, early detection, and aggressive treatment is critical. Table 1 lists the clinical studies of SA with CVD. The ratings for the quality of evidence was based upon the Oxford Center for Evidence-based Medicine's Levels of Evidence and Grades of Recommendation.

Prevention of CAD in SA

The conventional risk assessment tools may underestimate CVD risk in SA due to their premature disease onset.[59] SA have unwholesome diets rich in high fat dairy, butter, ghee, cheese, and paneer.[60] North Indians use saturated fats (ghee and butter), while South Indians use coconut oil for cooking.[59] Consequently, dietary counseling, lifestyle modification, and medical therapy should be instituted early. Encouragement of regular exercise (moderate or high intensity) with a reduction of a sedentary lifestyle, weight loss, smoking cessation, and increased consumption of fruits and vegetables may attenuate the progression of CAD. Patients should be counseled to consume a diet low in saturated fat, trans-fat, and processed foods. Moreover, if LDL is maintained ≤130 mg/dL, then elevated Lp(a)

Table 1. Clinical studies of South Asians, lipoprotein A, and cardiovascular disease

Study (type)	Patients (n)	Outcomes (follow-up)	Results	Level of Evidence Rating
INTERHEART Lp(a) Study[51] (international, standardized, case-control-2019)	6086 (initial MI), 6857 (controls)	Lp(a) concentration: first MI; 7 ethnicities (1829 South Asians) (no follow-up)	Africans highest Lp(a) = 27.2 mg/dL with population-attributable MI risk = 0%. South Asians = 18 mg/dL with population-attributable MI risk = 9.5%. High Lp(a) (>50 mg/dL) = > risk MI (high burden South Asians and Latin Americans)	3b
India-AMIYA Study[54] (single center, prospective-2017)	1116 STEMI patients (age $\leq$ 30)	Risk factors for MI, presentation, angiographic severity (in-hospital)	Risk factors: smoking, family history of premature CAD, obesity, physical inactivity, stressful life events; chest pain presentation; obstructive CAD (80.6%), single vessel (57.6%), double vessel (12.9%), left main (3.2%), LAD (58.1%), RCA (28.2%)	1b
Rajasekhar et al.[55] (case-control-2004)	200 (151 angiographic CAD; 49 controls)	Lp(a) concentrations and MI (no follow-up)	> Lp(a) = triple vessel and single vessel CAD ($P < 0.05$); Lp(a) > 25 mg/dL associated with CAD; Lp(a) correlates with vessel severity $P < 0.005$)	3b
Yusuf et al.[56] (prospective cross-sectional case-control -2014)	150 (single, double, triple vessel CAD); 150 controls	Lp(a) levels and link with CAD severity in North India (no follow-up)	Median Lp(a) > CAD patients vs controls (30.0 vs 20 mg/dL, $P < 0.001$); Lp(a) >40 mg/dL = independent CAD risk factor ($P < 0.001$); ACS Lp(a) > chronic stable angina (35.4 vs 23 mg/dL, $P <$ 0.001)	3b

(*continued on next page*)

Table 1. (*continued*)

Study (type)	Patients (n)	Outcomes (follow-up)	Results	Level of Evidence Rating
Gambhir et al.[57] (case-control-2008)	220: angiographic CAD (age<40); 160 controls	Lp(a) levels and link with family history of premature CAD in young North Indians (no follow-up)	Median Lp(a) > CAD patients vs controls (30 vs 12.7 mg/dL, $P < 0.05$); Lp (a) = independently associated with angiographic CAD	3b
Ashfaq et al.[58] (cross-sectional-2012)	360 coronary angiography (chest pain, acute MI, unstable/stable angina); 270 angiographic CAD	Lp(a) levels and link with CAD; North Indians (no follow-up)	Lp(a) levels > CAD vs no CAD patients (48.7 vs 18.9 mg/dL, $P < 0.0001$); Lp (a) levels severe CAD = 88.0 mg/dL; Lp (a): single, double, triple vessel CAD (39.3, 58.0, 69.2 mg/dL, $P < 0.05$); Lp (a) = causal independent CAD risk factor	4

ACS, acute coronary syndrome; CAD, coronary artery disease; India-AMIYA study, India-acute myocardial infarction in very young adults; LAD, left anterior descending artery; LPA, lipoprotein A; MI, myocardial infarction; RCA, right coronary artery; STEMI, ST segment elevation myocardial infarction.

may not have a significant effect on cardiovascular events (OR 1.20, 95% CI: 0.9 to 1.60, $P = 0.21$). Conversely, if LDL $\geq$ 130 md/dL, elevated Lp (a) may increase such risk (OR 1.46, 95% CI: 1.23 to 1.73, $P < 0.001$).[61] The GeneBank Study[37] showed that an LDL $\geq$70-100 mg/dL ($P = 0.049$) and >100 mg/dL ($P = 0.02$) with elevated Lp(a) was associated with worse cardiovascular outcomes. Whereas, LDL<70 mg/dL with an elevated Lp(a) showed no adverse outcomes. Hence, the exact LDL which portends CVD risk reduction is unclear. Therefore, the treatment approach for patients with elevated Lp(a) should target LDL reduction.

Education about their genetic proclivity and inheritance of CAD may stimulate a healthier lifestyle or induce early lifestyle modification. In high risk SA with normal or mildly abnormal lipid parameters, obtaining a Lp(a) level as a marker for increased CVD risk may be considered, so lifestyle modification and medical therapy can be implemented with elevated Lp(a). It might provide the impetus for further treatment if the patient is reluctant to contemplate lifestyle modification, statin therapy, and exercise therapy. Enas et al[62] recommends obtaining lipids in all Indians at age 20 or at age 10 with a family history of hyperlipidemia or CVD.

Treatment of Elevated Lp(a)

Treatment options are niacin, proprotein convertase subtilisin/kexin-type 9 (PCSK9) inhibitors, cholesterol ester transfer protein inhibitors, mipomersen (antisense oligonucleotide inhibitor), and lipoprotein apheresis. Niacin (1-3 grams/day) may lower Lp(a) by 20%-40%.[63] In an Indian study (n = 90), niacin monotherapy for 12 weeks reduced Lp(a) levels by 53.64%.[64] Unfortunately, niacin use is limited by adverse side effects such as flushing, dyspepsia, elevated alanine aminotransferase, and myalgias.[64] PCSK9 inhibitors may decrease Lp(a) up to 30%.[65,66] Stains may increase Lp(a) by 10%-20%.[13] In contrast, a prospective single-center study of 87 patients (follow-up of 6 months) with CAD or high-risk for CAD and Lp(a) of >50 mg/dL, rosuvastatin (n = 25, 18.2 $\pm$ 24.8, $P = 0.001$) produced a significant decrease in Lp(a) compared with atorvastatin (n = 22), atorvastatin plus fenofibrate (n = 20), or atorvastatin plus niacin (n = 20).[20] Lp(a) apheresis (extracorporeal elimination) is a therapeutic approach in which atherogenic Apo B-100, Lp(a), and LDL is removed from the blood or plasma.[67] It is the most effective method to reduce Lp(a) (>80% removal).[68]

The post-hoc analysis of the Familial Atherosclerosis Treatment Study (FATS)[69] of 146 men ($\leq$62 years, randomized, double blind, placebo

controlled study) with CAD and elevated Lp(a) (≥125 mg/dL) evaluated the effects of cholesterol reduction using lovastatin plus colestipol, niacin plus colestipol, or colestipol plus placebo. In patients with Lp(a) ≥90th percentile, reduction of elevated LDL had a substantial reduction in cardiac events (death, MI, and revascularization for refractory ischemia) and CAD. Thus, if LDL was substantially reduced, the persistent elevations of Lp(a) [not significantly affected by cholesterol treatment] was no longer atherogenic, nor associated with increased CVD risk. Almond consumption may be considered since it can reduce the total and LDL cholesterol, while increasing HDL.[70] Such cholesterol reduction is especially beneficial with elevated Lp(a). Consequently, LDL reduction is paramount to mitigate the risk of elevated Lp(a).

Discussion

SA comprise a large proportion of the world's population (24%) so increased SA CVD is a global concern. Approximately 5-10% of Indians have an MI younger than 40 years of age. MI can occur in SA about 5-10 years earlier than Caucasians. Such a large number of SA patients with premature heart disease can substantially effect their quality of life, work productivity, longevity, and future generations due to family history. Furthermore, since elevated Lp(a) is genetically determined, counseling in SA should involve the patient and family members to promote healthier habits and lifestyles.

Epidemiological and meta-analysis have provided causal evidence of elevated Lp(a) and enhanced CVD risk. However, most of the data is derived from Caucasian who have lower median Lp(a) levels and MI at a later age compared with SA. Thus, their data cannot be extrapolated to SA who have various risk factors and higher Lp(a) levels so long-term randomized studies are necessary in SA. SA have insalubrious diets and increased Lp(a) which augments their risk for MI, premature CAD, multivessel CAD, mortality post-PCI, mortality while on statins, and long-term mortality. Hence, SA with high LDL and elevated Lp(a) should be aggressively treated to reduce lipids and CVD risk. If LDL is optimally controlled, elevated Lp(a) may not be as deleterious. Aggressive risk factor modification, early initiation of lipid lowering therapy, dietary counseling, smoking cessation, and regular exercise may diminish their risk.

SA ethnicity has been recognized as a risk enhancer for CVD in the 2019 American College of Cardiology (ACC)/American Heart Association (AHA) Guideline on the Primary Prevention of CVD.[71] The 2018

Society Guideline on the Management of Blood Cholesterol[72] and the 2019 ACC/AHA Guideline on the Primary Prevention of CVD[71] lists Lp (a) as a risk enhancer for CVD.

Lp(a) screening may provide valuable information in patients with premature CAD, MI, family history of MI, familial hypercholesterolemia, or CVD risk factors. In patients with normal lipids and CAD or acute MI, Lp(a) screening may be considered. Treatment for elevated Lp(a) is limited to niacin, statins, LP(A) apheresis, and PCSK9 inhibitors. Nevertheless, precise treatment recommendation for Lp(a) reduction cannot be provided due to the deficiency of robust clinical data.

Limitations of this review include a dearth of randomized clinical data in SA with elevated Lp(a). Gaps in knowledge include the reason for dysfunctional HDL and genetic factors causing elevated Lp(a) in SA. Most of the clinical data is from Caucasians, who have lower Lp(a) levels, lipids, and risk factors. Thus, randomized controlled, multicenter, or prospective studies with long-term follow-up may be beneficial in SA to understand their pathophysiology for CAD. Subsequently, optimal prevention and treatment can be initiated in SA who have a high propensity for CVD. Clinical data in Lp(a) treatment and CV outcomes is sparse so targeted therapies for Lp(a) may provide an area of research.

Conclusions

Elevated Lp(a) is associated with an amplified risk of premature CAD, severity of CAD, multivessel CAD, MI, and long-term mortality in SA. Targeted medical therapy is limited. Optimal treatment of LDL, lipid management, aggressive lifestyle modification, dietary counseling, smoking cessation, and regular exercise is critical.

REFERENCES

1. Bilen O, Kamal A, Virani SS. Lipoprotein abnormalities in South Asians and its association with cardiovascular disease: current state and future directions. *World J Cardiol* 2016;8:247–57.
2. Nishtar S. Prevention of coronary heart disease in south Asia. *Lancet* 2002;360:1015–8.
3. Anand SS, Yusuf S, Vuksan V, et al. Differences in risk factors, atherosclerosis, and cardiovascular disease between ethnic groups in Canada: the Study of Health Assessment and Risk in Ethnic groups (SHARE). *Lancet* 2000;356:279–84.
4. Mohan V, Deepa R, Rani SS, Premalatha G, Chennai Urban Population S. Prevalence of coronary artery disease and its relationship to lipids in a selected population in South India: The Chennai Urban Population Study (CUPS No. 5). *J Am Coll Cardiol* 2001;38:682–7.

5. Lee J, Heng D, Chia KS, Chew SK, Tan BY, Hughes K. Risk factors and incident coronary heart disease in Chinese, Malay and Asian Indian males: the Singapore Cardiovascular Cohort Study. *Int J Epidemiol* 2001;30:983–8.
6. Balarajan R. Ethnic differences in mortality from ischaemic heart disease and cerebrovascular disease in England and Wales. *BMJ* 1991;302:560–4.
7. Enas EA, Mehta J. Malignant coronary artery disease in young Asian Indians: thoughts on pathogenesis, prevention, and therapy. Coronary Artery Disease in Asian Indians (CADI) Study. *Clin Cardiol* 1995;18:131–5.
8. Yusuf S, Hawken S, Ounpuu S, et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. *Lancet* 2004;364:937–52.
9. Joshi P, Islam S, Pais P, et al. Risk factors for early myocardial infarction in South Asians compared with individuals in other countries. *JAMA* 2007;297:286–94.
10. Berglund L, Ramakrishnan R. Lipoprotein(a): an elusive cardiovascular risk factor. *Arterioscler Thromb Vasc Biol* 2004;24:2219–26.
11. Manocha A, Srivastava LM. Lipoprotein (a): a unique independent risk factor for coronary artery disease. *Indian J Clin Biochem* 2016;31:13–20.
12. Kronenberg F. Human genetics and the causal role of lipoprotein(a) for various diseases. *Cardiovasc Drugs Ther* 2016;30:87–100.
13. Tsimikas S. A test in context: lipoprotein(a): diagnosis, prognosis, controversies, and emerging therapies. *J Am Coll Cardiol* 2017;69:692–711.
14. Marcovina SM, Koschinsky ML, Albers JJ, Skarlatos S. Report of the National Heart, Lung, and Blood Institute workshop on lipoprotein(a) and cardiovascular disease: recent advances and future directions. *Clin Chem* 2003;49:1785–96.
15. Tsimikas S, Fazio S, Ferdinand KC, et al. NHLBI working group recommendations to reduce lipoprotein(a)-mediated risk of cardiovascular disease and aortic stenosis. *J Am Coll Cardiol* 2018;71:177–92.
16. Anuurad E, Enkhmaa B, Berglund L. Enigmatic role of lipoprotein(a) in cardiovascular disease. *Clin Transl Sci* 2010;3:327–32.
17. Bennet A, Di Angelantonio E, Erqou S, et al. Lipoprotein(a) levels and risk of future coronary heart disease: large-scale prospective data. *Arch Intern Med* 2008;168:598–608.
18. Kamstrup PR, Tybjaerg-Hansen A, Steffensen R, Nordestgaard BG. Genetically elevated lipoprotein(a) and increased risk of myocardial infarction. *JAMA* 2009;301:2331–9.
19. Clarke R, Peden JF, Hopewell JC, et al. Genetic variants associated with Lp(a) lipoprotein level and coronary disease. *N Engl J Med* 2009;361:2518–28.
20. Vavlukis M, Mladenovska K, Daka A, et al. Effects of rosuvastatin versus atorvastatin, alone or in combination, on lipoprotein (a). *Ann Pharmacother* 2016;50:609–15.
21. Hoogeveen RC, Gambhir JK, Gambhir DS, et al. Evaluation of Lp[a] and other independent risk factors for CHD in Asian Indians and their USA counterparts. *J Lipid Res* 2001;42:631–8.
22. Sandholzer C, Boerwinkle E, Saha N, Tong MC, Utermann G. Apolipoprotein(a) phenotypes, Lp(a) concentration and plasma lipid levels in relation to coronary heart

disease in a Chinese population: evidence for the role of the apo(a) gene in coronary heart disease. *J Clin Invest* 1992;89:1040–6.
23. Bostom AG, Cupples LA, Jenner JL, et al. Elevated plasma lipoprotein(a) and coronary heart disease in men aged 55 years and younger. A prospective study. *JAMA* 1996;276:544–8.
24. Saeedi R, Frohlich J. Lipoprotein (a), an independent cardiovascular risk marker. *Clin Diabetes Endocrinol* 2016;2:7.
25. Sairam SG, Sola S, Barooah A, et al. The role of Lp-PLA2 and biochemistry parameters as potential biomarkers of coronary artery disease in Asian South-Indians: a case-control study. *Cardiovasc Diagn Ther* 2017;7:589–97.
26. Tsimikas S. Lipoprotein(a): novel target and emergence of novel therapies to lower cardiovascular disease risk. *Curr Opin Endocrinol Diabetes Obes* 2016;23:157–64.
27. Kamstrup PR. Lipoprotein(a) and ischemic heart disease−a causal association? A review. *Atherosclerosis* 2010;211:15–23.
28. Enas EA, Varkey B, Dharmarajan TS, Pare G, Bahl VK. Lipoprotein(a): an independent, genetic, and causal factor for cardiovascular disease and acute myocardial infarction. *Indian Heart J* 2019;71:99–112.
29. Wang JJ, Zhang CN, Meng Y, Han AZ, Gong JB, Li K. Elevated concentrations of oxidized lipoprotein(a) are associated with the presence and severity of acute coronary syndromes. *Clin Chim Acta* 2009;408:79–82.
30. Malaguarnera M, Vacante M, Russo C, et al. Lipoprotein(a) in cardiovascular diseases. *Biomed Res Int* 2013;2013:650989.
31. Cai A, Li L, Zhang Y, Mo Y, Mai W, Zhou Y. Lipoprotein(a): a promising marker for residual cardiovascular risk assessment. *Dis Markers* 2013;35:551–9.
32. Nordestgaard BG, Langsted A. Lipoprotein(a): as a cause of cardiovascular disease: insights from epidemiology, genetics, and biology. *J Lipid Res* 2016;57:1953–75.
33. Kamstrup PR, Tybjaerg-Hansen A, Nordestgaard BG. Extreme lipoprotein(a) levels and improved cardiovascular risk prediction. *J Am Coll Cardiol* 2013;61:1146–56.
34. Armstrong VW, Cremer P, Eberle E, et al. The association between serum Lp(a) concentrations and angiographically assessed coronary atherosclerosis. Dependence on serum LDL levels. *Atherosclerosis* 1986;62:249–57.
35. Schwartzman RA, Cox ID, Poloniecki J, Crook R, Seymour CA, Kaski JC. Elevated plasma lipoprotein(a) is associated with coronary artery disease in patients with chronic stable angina pectoris. *J Am Coll Cardiol* 1998;31:1260–6.
36. Nordestgaard BG, Chapman MJ, Ray K, et al. Lipoprotein(a) as a cardiovascular risk factor: current status. *Eur Heart J* 2010;31:2844–53.
37. Nicholls SJ, Tang WH, Scoffone H, et al. Lipoprotein(a) levels and long-term cardiovascular risk in the contemporary era of statin therapy. *J Lipid Res* 2010;51:3055–61.
38. Foody JM, Milberg JA, Pearce GL, Sprecher DL. Lipoprotein(a) associated with coronary artery disease in older women: age and gender analysis. *Atherosclerosis* 2000;153:445–51.
39. Suwa S, Ogita M, Miyauchi K, et al. Impact of lipoprotein(a) on long-term outcomes in patients with coronary artery disease treated with statin after a first percutaneous coronary intervention. *J Atheroscler Thromb* 2017;24:1125–31.

40. Feng Z, Li HL, Bei WJ, et al. Association of lipoprotein(a) with long-term mortality following coronary angiography or percutaneous coronary intervention. *Clin Cardiol* 2017;40:674–8.
41. Konig M, Joshi S, Leistner DM, et al. Cohort profile: role of lipoproteins in cardiovascular disease-the LipidCardio study. *BMJ Open* 2019;9:e030097.
42. Wang Z, Zhai X, Xue M, Cheng W, Hu H. Prognostic value of lipoprotein (a) level in patients with coronary artery disease: a meta-analysis. *Lipids Health Dis* 2019;18:150.
43. Kwon SW, Lee BK, Hong BK, et al. Prognostic significance of elevated lipoprotein (a) in coronary artery revascularization patients. *Int J Cardiol* 2013;167:1990–4.
44. Bedi US, Singh S, Syed A, Aryafar H, Arora R. Coronary artery disease in South Asians: an emerging risk group. *Cardiol Rev* 2006;14:74–80.
45. McKeigue PM, Miller GJ, Marmot MG. Coronary heart disease in south Asians overseas: a review. *J Clin Epidemiol* 1989;42:597–609.
46. Bhopal R, Unwin N, White M, et al. Heterogeneity of coronary heart disease risk factors in Indian, Pakistani, Bangladeshi, and European origin populations: cross sectional study. *BMJ* 1999;319:215–20.
47. Kalita S, Khandelwal S, Madan J, Pandya H, Sesikeran B, Krishnaswamy K. Almonds and cardiovascular health: a review. *Nutrients* 2018;10.
48. Sharma M, Ganguly NK. Premature coronary artery disease in Indians and its associated risk factors. *Vasc Health Risk Manag* 2005;1:217–25.
49. Aggarwal A, Aggarwal S, Goel A, Sharma V, Dwivedi S. A retrospective case-control study of modifiable risk factors and cutaneous markers in Indian patients with young coronary artery disease. *JRSM Cardiovasc Dis* 2012;1:1–8.
50. Cicek H, Bayil S, Zer Y, Celik A, Geyikli I. Comparison of lipoprotein(a) levels between elderly and middle-aged men with coronary artery disease. *Ann N Y Acad Sci* 2007;1100:179–84.
51. Pare G, Caku A, McQueen M, et al. Lipoprotein(a) levels and the risk of myocardial infarction among 7 ethnic groups. *Circulation* 2019;139:1472–82.
52. Tan ST, Scott W, Panoulas V, et al. Coronary heart disease in Indian Asians. *Glob Cardiol Sci Pract* 2014;2014:13–23.
53. Rao VS, Khadrinarasimhaih NB, Kanjilal S, Mukerjee M, Kakkar VV. Genetic contribution to variation in atherothrombotic phenotypes in the Asian Indian population. The Indian Atherosclerosis Research Study. *Thromb Haemost* 2009;102:379–88.
54. Sinha SK, Krishna V, Thakur R, et al. Acute myocardial infarction in very young adults: a clinical presentation, risk factors, hospital outcome index, and their angiographic characteristics in North India-AMIYA Study. *ARYA Atheroscler* 2017;13:79–87.
55. Rajasekhar D, Saibaba KS, Srinivasa Rao PV, Latheef SA, Subramanyam G. Lipoprotein (A): better assessor of coronary heart disease risk in South Indian population. *Indian J Clin Biochem* 2004;19:53–9.
56. Yusuf J, Yadav N, Mukhopadhyay S, et al. Relook at lipoprotein (A): independent risk factor of coronary artery disease in North Indian population. *Indian Heart J* 2014;66:272–9.

57. Gambhir JK, Kaur H, Prabhu KM, Morrisett JD, Gambhir DS. Association between lipoprotein(a) levels, apo(a) isoforms and family history of premature CAD in young Asian Indians. *Clin Biochem* 2008;41:453–8.
58. Ashfaq F, Goel PK, Moorthy N, Sethi R, Khan MI, Idris MZ. Lipoprotein(a) and SYNTAX score association with severity of coronary artery atherosclerosis in North India. *Sultan Qaboos Univ Med J* 2012;12:465–72.
59. Chandra KS, Bansal M, Nair T, et al. Consensus statement on management of dyslipidemia in Indian subjects. *Indian Heart J* 2014;66(Suppl 3):S1–51.
60. Ardeshna DR, Bob-Manuel T, Nanda A, et al. Asian-Indians: a review of coronary artery disease in this understudied cohort in the United States. *Ann Transl Med* 2018;6:12.
61. O'Donoghue ML, Morrow DA, Tsimikas S, et al. Lipoprotein(a) for risk assessment in patients with established coronary artery disease. *J Am Coll Cardiol* 2014;63:520–7.
62. Enas EA, Dharmarajan TS, Varkey B. Consensus statement on the management of dyslipidemia in Indian subjects: a different perspective. *Indian Heart J* 2015;67:95–102.
63. National Cholesterol Education Program Expert Panel on Detection E. Treatment of High Blood Cholesterol in A. Third report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III) final report. *Circulation* 2002;106:3143–421.
64. Kaur K, Rai J, Sharma G, Bal BS. An open-label comparison of the effects of simvastatin and niacin alone and combined on the lipid profile and lipoprotein (a) level in an Indian population with dyslipidemia. *Curr Ther Res Clin Exp* 2004;65:455–69.
65. Kotani K, Banach M. Lipoprotein(a) and inhibitors of proprotein convertase subtilisin/kexin type 9. *J Thorac Dis* 2017;9:E78–82.
66. Sahebkar A, Watts GF. New therapies targeting apoB metabolism for high-risk patients with inherited dyslipidaemias: what can the clinician expect? *Cardiovasc Drugs Ther* 2013;27:559–67.
67. Khan TZ, Pottle A, Pennell DJ, Barbir MS. The expanding role of lipoprotein apheresis in the treatment of raised lipoprotein(a) in ischaemic heart disease and refractory angina. *Glob Cardiol Sci Pract* 2014;2014:3–12.
68. Borberg H. Comparison of different Lp (a) elimination techniques: a retrospective evaluation. *Transfus Apher Sci* 2009;41:61–5.
69. Maher VM, Brown BG, Marcovina SM, Hillger LA, Zhao XQ, Albers JJ. Effects of lowering elevated LDL cholesterol on the cardiovascular risk of lipoprotein(a). *JAMA* 1995;274:1771–4.
70. Sabate J, Haddad E, Tanzman JS, Jambazian P, Rajaram S. Serum lipid response to the graduated enrichment of a Step I diet with almonds: a randomized feeding trial. *Am J Clin Nutr* 2003;77:1379–84.
71. Arnett DK, Blumenthal RS, Albert MA, et al. 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease: a report of the American College of Cardiology/American Heart Association Task Force on clinical practice guidelines. *J Am Coll Cardiol* 2019;74:e177–232.

72. Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: a report of the American College of Cardiology/American Heart Association Task Force on clinical practice guidelines. *J Am Coll Cardiol* 2019;73:e285–350.