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Curbside Consults

Consideration and Application of Lipoprotein(a) in the Risk Assessment of Atherosclerotic Cardiovascular Disease Risk in Adults

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ABSTRACT

Lipoprotein(a) (Lp[a]) is an low-density lipoprotein (LDL)-like particle in which apolipoprotein (apo) B is covalently bound to a plasminogen-like molecule called apo(a). A High level of Lp(a) has been demonstrated to be an independent, causal, and prevalent risk factor for atherosclerotic cardiovascular disease (ASCVD), as well as aortic valve disease, through mechanisms that promote atherogenesis, inflammation, and thrombosis. With reliable and accessible assays, Lp(a) level has been established to be associated linearly with the risk for ASCVD. The 2021 Canadian Cardiovascular Society Dyslipidemia Guidelines recommend measuring an Lp(a) level once in a person's lifetime as part of the initial lipid screening. The aim of this review is to provide an update and overview of the utility and application of Lp(a) level in the assessment and treatment of adults at risk for ASCVD, consistent with this guideline recommendation.

RÉSUMÉ

La lipoprotéine(a), ou Lp(a), est une lipoprotéine de basse densité dans laquelle l'apolipoprotéine B est liée de manière covalente à une molécule semblable au plasminogène, l'apolipoprotéine(a). On a démontré qu'un taux élevé de Lp(a) est un facteur de risque indépendant, causal et fréquent d'athérosclérose cardiovasculaire (ASCV) et de valvulopathie aortique, en raison de mécanismes qui favorisent l'athérogénèse, l'inflammation et la thrombose. Des épreuves fiables et accessibles ont permis d'établir que le taux de Lp(a) était associé de façon linéaire à un risque d'ASCV. Dans ses lignes directrices de 2021 sur la prise en charge de la dyslipidémie, la Société cardiovasculaire du Canada recommande de mesurer le taux de Lp(a) une fois au cours de la vie d'une personne, dans le cadre du dépistage initial des lipides. Le présent article vise à fournir une mise à jour et un compte rendu de l'utilité et de l'application du taux de Lp(a) dans l'évaluation et le traitement des adultes présentant un risque d'ASCV, conformément à cette recommandation issue des lignes directrices.

Cardiovascular (CV) diseases consistently rank among the leading causes of morbidity and mortality in Canada. In a concerted effort to combat this issue, improvements have been made in the management of myocardial infarctions (MIs), including more effective medical therapy and advancements in both percutaneous coronary interventions and surgical management. Efforts also have included an increasing focus on pre-hospital care, including early detection and treatment of atherosclerotic CV disease (ASCVD) and aggressive risk-factor control. Despite this focus, Canadians continue to experience the complications of ASCVD, including MIs, strokes, and peripheral vascular disease, at high rates. This situation underscores a need to comprehensively assess not only traditional but also emerging and novel risk factors, to improve preventive cardiology.

Lipid management is a central strategy for cardiac risk reduction. Treatment and adequacy of lipid control are assessed through standard serum lipid panels. Traditionally, a lipid panel separates lipids into 3 variables: low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglycerides (TGs). Prior research has demonstrated that lipid particles containing apolipoprotein (apo) B-100 (apo B), such as LDL-C, are linked with an increased risk of ASCVD.[1-3] Although lipoprotein a (Lp[a]) was not routinely tested previously, the 2021 Canadian

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Cardiovascular Society (CCS) Dyslipidemia Guidelines now recommend that the level of Lp(a), an apo B−containing particle, be measured once in a patient's lifetime, to further stratify ASCVD risk.[4]

Lp(a) has been a long-recognized, but not previously well understood, entity in lipid research. First described in Scandinavian blood bank samples in 1963,[5] Lp(a) subsequently was found to be related to lipids and ASCVD risk.[6] Recent research has suggested that a causal link exists between elevated Lp(a) concentrations and increased ASCVD risk.[7-10] Furthermore, familial studies of Lp(a) concentrations and protein isoforms have revealed clear inheritance patterns, showing a strong genetic determination of overall Lp(a) levels, technically following autosomal codominant inheritance.[11-13] The clinical utility of Lp(a) and the possibility of targeted therapy remain areas of active research. In this review, we present 2 interesting case studies, with an overview of Lp(a) and its potential current application to individualizing cardiac risk assessment for patients.

Lp(a)

Composition, synthesis, and catabolism

Lp(a) is composed of an LDL-like particle with one apoB and one apo(a) molecule.[1] ApoB, synthesized and released by the liver, has a molecular weight of 540 kDa. Apo(a) is similarly synthesized and released by the liver. However, apo(a) exists as one of over 40 different-size isoforms of variable molecular weights due to variable numbers of repeated kringle IV type 2 (KIV-2) domains, which resemble homologous domains in plasminogen, so named because they resemble the Danish pretzel-like pastry called a "kringle." The rate of Lp(a) production is inversely related to the size of the isoform. Lp(a) particles containing smaller apo(a) isoforms are assembled and secreted more efficiently and are degraded more slowly than particles containing larger isoforms."[14] Given this, the concentration of serum Lp(a) can vary by as much as 1000-fold.[14]

The assembly of Lp(a) consists of 2 covalently linked disulphide bonds between apoB and apo(a), occuring either within the liver or in the systemic circulation.[15] Catabolism of purely apoB-containing particles, such as LDL, occurs primarily in the liver, but the site of catabolism of apoB plus apo(a) in Lp(a) particles remains controversial, with both the liver and kidneys being proposed sites.[16] Regardless of the site(s) of catabolism, the overall serum concentration of Lp(a) is influenced predominantly by the rate of particle production and not by the rate of catabolism.[14]

Genetics

Lp(a) levels are controlled primarily by the *LPA* gene on chromosome 6q25 and are grossly unaffected by other patient characteristics, such as age, sex, systemic inflammation, and lifestyle.[16-18] Although diet and certain medical conditions, such as liver failure and renal insufficiency, may influence Lp(a) levels, these associations are not as well characterized.[18,19] DNA copy number variation within *LPA* determines the number of KIV-2 repeats in the apo(a) protein.[13,20,21] This number, in turn, affects the overall concentration of Lp(a), with a low number of KIV2 repeats coding for small and quickly synthesized apo(a) isoforms, resulting in higher serum Lp(a) concentrations, and a higher number of KIV-2 repeats coding for larger and slow-to-synthesize apo(a) isoforms, resulting in comparatively lower serum Lp(a) concentrations.[8]

Genomic studies have further identified variants responsible for the different expression of Lp(a) across and within populations. As an example, 3 single-nucleotide polymorphisms (SNPs) have been identified as one cause of different Lp(a) levels in Black vs White populations. T3888P and G+1/inKIV-8A, more common in White populations, suppress the assembly of Lp(a), whereas G-21A, more common in Black populations, increases apo(a) promoter activity. Two other SNPs, rs10455872 and rs3798220, are thought to code for smaller apo(a) isoforms.[22] Different polynucleotide repeats in the *LPA* promoter region have resulted in a 14% variation in Lp(a) levels in White populations.[23] Over 500 other variants of *LPA* have been associated with Lp(a) concentrations, highlighting the major role of genetics in the expression of this lipid biomarker. However, the most important genetic determinant of Lp(a), by several orders of magnitude more than individual SNPs, is the *LPA* copy number variation that codes for apo(a) size isoforms. Variation at other genes, including *APOE*, *CETP*, and *APOH* also have been found to have very minor effects on Lp(a) concentrations.[24-26] Research is ongoing to uncover other genes and genetic variants that affect the expression of Lp(a). These genetic factors determine from birth the level of Lp(a), and hence the lifetime CV risk of Lp(a) in individuals. This context provides a rationale for measurement of Lp(a) at least once in a person's lifetime, in concert with a standard lipid panel. An important point to recognize is that although Lp(a) is an apoB-containing particle, whether the level of Lp(a) is elevated or normal cannot be deduced from apoB or any other component of the traditional lipid panel.

Epidemiology

Lp(a) concentrations in the population follow a highly rightward-skewed Gaussian distribution, with the large majority of people having low Lp(a) concentrations. Depending on the cutpoint used to define a "high" level, 20% of the world's population has an elevated level, translating into a $>$ 20% increase in risk (ie, an odds ratio of 1.2) of cardiac morbidity and mortality.[27,28] The risk of major CV events increases by 2-2.5 times for patients with Lp(a) levels greater than the 95th and 99th percentiles, repsectively. The distribution of Lp(a) levels differs across ethnic backgrounds, with the highest median levels occurring in Black populations, followed by South Asian, White, and Chinese populations.[13,19,29,30]

In populations without established ASCVD, large epidemiologic studies have revealed an elevated Lp(a) level to be linked causally to the subsequent development of ASCVD, with every 2-fold increase in Lp(a) level translating to a 22% increased risk of MI.[31,32] An elevated Lp(a) level also is thought to cause accelerated micro- and macro-calcification of the aortic valve, increasing the risk of aortic stenosis and the need for valvular intervention.[33,34] Lp(a) levels greater than the 90th and 95th percentile were associated with a higher risk of heart failure (odds ratio of 1.57 [confidence interval 1.32-1.87]) and of ischemic stroke (hazard ratio of 1.60 [confidence interval 1.24-2.05]), respectively.[35-38]

Table 1. Current lipid therapies and their effects on lipoprotein a (Lp[a]) levels

Drug name/class	Mechanism of action	Target organ	Market availability	Effect on Lp(a) levels
Statins	HMG-CoA Reductase inhibitor	Liver	Approved	Increases by 10%-20%, depending on agent
Ezetimibe	NPC1L1 inhibitor	Intestines	Approved	No effect
Niacin	DGAT-2 inhibitor	Liver	Approved	Decreases by 15%-20%
Lipid apheresis	Centrifugation or filtration	N/A	Approved in US	Decreases by ~60% post-apheresis
PCSK9 inhibitors	PCSK9 inhibitor	Liver	Approved	Decreases by ~25%
Inclisiran	siRNA to PCSK9	Liver	Approved	Decreases by ~20%–25%
Pelacarsen	Antisense oligonucleotide to LPA	Liver	In development	Decreases by ~80%
Olpasiran	siRNA to LPA	Liver	In development	Decreases by ~90%
Muvalaplin	Oral small molecule that inhibits Lp(a) formation by blocking the apo(a)-apo B100 interaction	Liver	In development	Decreases by 63%–65%

apo, apolipoprotein; DGAT-2, diacylglycerol O-acyltransferase 2; HMG-CoA, β-Hydroxy β-methylglutaryl-CoA; Lp(a), lipoprotein (a); LPA, apolipoprotein(a) gene; N/A, not applicable; NPC1L1, Niemann-Pick C1-Like 1; PCSK9, proprotein convertase subtilisin/kexin type 9; siRNA, small interfering RNA.
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Globally, the Lp(a)HERITAGE study found elevated Lp(a) levels in ~25% of the population with established ASCVD. Lp(a) and LDL-C levels were higher in women and younger patients, reflecting the potential influence of these lipoproteins on development of premature ASCVD.[39] Elevated Lp(a) levels in this population are associated with an increased risk of major adverse cardiovascular events (MACE). Notably, this study found that only 14% of patients with ASCVD had known Lp(a) levels prior to the study.

Current understanding of the pathophysiology of Lp(a) and ASCVD

Although the causal link between an elevated Lp(a) level and the risk of ASCVD has been established by epidemiologic studies, and indirectly by Mendelian randomization studies, our understanding of its pathophysiology is still evolving. Lp(a) is thought to have prothrombotic, proinflammatory, and other proatherogenic effects, although the exact mechanisms are unclear.[7,16,40]

Prior *in vitro* studies have shown that the apo(a) moiety in Lp(a) prevents fibrinolysis competitively inhibiting the binding of plasminogen to endothelial cells, monocytes, fibrin, and platelets.[41-45] In a normal process of fibrinolysis, plasminogen is cleaved into plasmin by tissue-type plasminogen activator or urokinase-type plasminogen activator. Plasmin then preferentially binds fibrin at lysine-binding sites, solubilizing it. Protein sequence analysis has demonstrated extensive structural similarities between apo(a) and plasminogen, revealing a strong lysine-binding site on apo(a) that can block sites on fibrin, preventing the binding of plasmin to fibrin.[40] Surprisingly, lowering Lp(a) levels with antisense oligonucleotides directed at *LPA* mRNA did not influence *ex vivo* plasma clot lysis times.[46] Further, elevated Lp(a) levels have not been found to reduce the efficacy of thrombolytic therapy, although these findings were reported only in a series of small studies.[47-52] Conversely, studies with expression of apo(a) in transgenic mice did result in reduced fibrinolysis.[53] These conflicting data seem to suggest a prothrombotic effect of Lp(a) that extends beyond its antifibrinolytic properties. Ongoing studies to fully elucidate these effects are needed.

The exact role of Lp(a) in atherogenesis is also unclear. Evidence is growing that Lp(a) may have strong proinflammatory effects, due to the many oxidized phospholipids (OxPLs) on its apo(a) tail, with *in vitro* studies demonstrating activation of endothelial cell inflammatory pathways after exposure to higher concentrations of Lp(a). Thus, a higher concentration of Lp(a) is theorized to initiate endothelial damage through the inflammatory cascade.[54] Lp(a) is also a carrier of autotaxin (ATX), a phospholipid that has been shown to promote inflammation and fibrosis, and in a small study, has been shown to be associated with calcified aortic stenosis at higher concentrations.[55] The strong binding between apo(a) and fibrin also has been suggested to be a mechanism that increases delivery and accumulation of cholesterol to the arterial intima, downregulation of plasmin, and smooth muscle cell proliferation.[56]

Although these associations have been proposed as possible mechanisms for increased ASCVD risk or accelerated atherosclerosis and aortic calcification,[40,54,55] still lacking is a

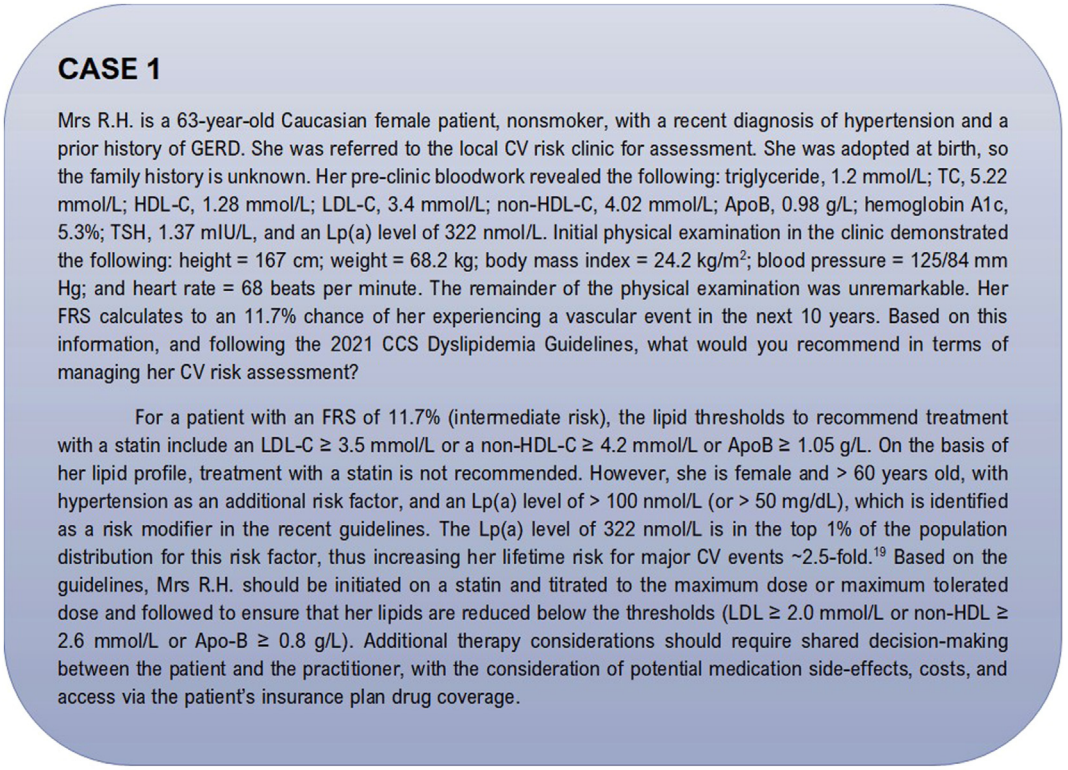

Figure 1. Case 1: Primary prevention patient with intermediate level of risk. ApoB, apolipoprotein B; CCS, Canadian Cardiovascular Society; CV, cardiovascular; FRS, Framingham Risk Score; GERD, gastroesophageal reflux disease; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein A; TC, total cholesterol; TSH, thyroid-stimulating hormone.

definitive mechanistic understanding of how Lp(a) drives the increased risk. Studies to generate a clearer understanding of this process are ongoing.

Current guideline recommendations

Preventive CV medicine begins with screening for risk factors and is often combined with health-behaviour modifications. To stratify one's lifetime risk of ASCVD, the 2021 CCS Guidelines for Management of Dyslipidemia recommend performing a one-time measurement of Lp(a) during a person's lifetime, along with a clinical history and a physical examination, a standard lipid panel, a diabetes screen with fasting plasma glucose or hemoglobin (Hb)A1c level, and a renal assessment with estimated glomerular filtration rate.[4] These guidelines echo the 2019 recommendations from the European Society of Cardiology.[57] Presently, the American College of Cardiology/American Heart Association guideline does not recommend routine measurement of Lp(a), although a strong family history of ASCVD is listed as a possible indication for measurement of this lipoprotein.[58]

Lp(a) levels have not been found to markedly improve risk discrimination when used in risk-assessment algorithms, such as the Framingham Risk Score, the Reynolds Risk Score, or the European Society of Cardiology (ESC) **S**ystematic **Co**ronary **R**isk **E**valuation (SCORE) model.[28,59,60] This lack of improvement may, in part, be due to the dose-dependent relationship between Lp(a) levels and ASCVD risk. As Lp(a) levels increase to over 30 mg/dL (~60-75 nmol/L), ASCVD risk also rises in a dose-dependent fashion. Presently, the 2021 CCS Dyslipidemia Guidelines recommend that in primary prevention, individuals with Lp(a) levels ≥ 50 mg/dL (~100 nmol/L) receive earlier and more intensive counselling and management of their ASCVD risk.[4] Overall, the proposed approach to interpreting Lp(a) levels is to combine the Lp(a) level with an individual's baseline global risk of ASCVD. For example, an Lp(a) level of 100 mg/dL (~250 nmol/L) nearly doubles the risk of ASCVD, regardless of the baseline risk. The magnitude of absolute ASCVD risk, however, is greater in those with a higher baseline risk, compared to that in those with a lower baseline risk. Thus, currently Lp(a) is considered a "risk enhancer." In light of the known differences in Lp(a) levels across ethnic populations, this global assessment is recommended to personalize patients' risk management.[19]

Challenges in clinical utility

The varying molecular weights of apo(a) isoforms, compounded by the fact that any given individual may carry 2 different apo(a) alleles with variable expression, once provided a challenge for accurate and standardized testing in the general population.[7] The current assays available across Canada, however, have proven to be sensitive to differing apo(a) isoforms, which artifactually compromise accurate quantification by antibody or chemical methods. The remaining ongoing challenge is assessing the significance of measured values. In studies comparing unrelated patients with the same apo(a)

CASE 2

Mr L.P., a 48-year-old male nonsmoker of South Asian descent, was referred for ASCVD assessment, prompted by a new RBBB with mild repolarization abnormalities incidentally found on an ECG completed for an insurance medical examination. Prior to his assessment, he was referred for a cardiac PET/CT which revealed the following: (i) no ischemic symptoms or ECG changes with dipyridamole stress; (ii) normal myocardial perfusion with no fixed or reversible perfusion abnormalities; (iii) a LV ejection fraction > 65%, no wall-motion abnormalities, and normal LV volumes.

His ASCVD screening blood work revealed the following results: TG, 2.1 mmol/L; TC, 7.24 mmol/L; HDL-C, 1.07 mmol/L; LDL-C, 5.22 mmol/L; non-HDL-C, 6.17 mmol/L, and hemoglobin A1c, 5.8%. Initial physical examination in the clinic demonstrated the following: height = 180 cm; weight = 98.2 kg; BMI = 30.3 kg/m^2; blood pressure = 122/82 mm Hg; and heart rate = 84 beats per minute. The remainder of his physical examination was unremarkable, and negative for any physical stigmata of hypercholesterolemia (ie, no corneal arcus, xanthelasmas, or tendon xanthomas). He reported a history of nonpremature ASCVD in his father who had coronary artery bypass grafting surgery at the age of 72 years. Otherwise, no additional contributory family history was noted. He was not treated with any medications.

On the basis of these data, his FRS was calculated at 9.4%, predicting that he would be at low risk for experiencing an ASCVD event over the next 10 years. His elevated LDL-C level of 5.47 mmol/L, however, indicated that he had a "statin-indicated condition."[4] To further support the initiation of statin therapy, the potential diagnosis of FH was entertained. Using the DCLN for FH, however, Mr L.P. only had a "possible" clinical diagnosis of FH based on his LDL-C level being > 5.0 mmol/L. After discussion, Mr L.P. opted for lifestyle modification (diet, exercise, and weight loss) over statin therapy initiation.

Although he was resistant to starting a statin, he agreed to undergo testing for FH, which did not detect any pathogenic variants in causal genes for FH failing to support a diagnosis of heterozygous FH. At his follow-up appointment 3 months later, Mr L.P. had a repeat lipid panel to assess the efficacy of his lifestyle changes. Despite his losing nearly 4.5 kgs in weight, and decreasing his BMI to 29 kg/m^2, the results of his repeat lipid panel were nearly identical to those of his first, but the Lp(a) level ordered was reported as 215 nmol/L. This Lp(a) level places him well above the 95th percentile for the population distribution of this lipoprotein, which is associated with an ~2.5-fold increased risk of myocardial infarction.[31] Lp(a) levels greater than the 90th and 95th percentile also have been associated with higher risk of heart failure and ischemic stroke, respectively.[35-38] These risks are independent of the risk of ASCVD events predicted by other tools, such as the FRS.

Statin-hesitant patients, particularly primary prevention patients such as Mr L.P., occasionally require additional evidence of the benefits of statins beyond what standard risk-prediction tools such as the FRS can provide. Although further evidence that directly lowering Lp(a) level reduces ASCVD risk is pending, a high Lp(a) level should alert practitioners to actively pursue an overall ASCVD event risk assessment, earlier introduction of a statin, or other appropriate lipid-lowering therapies when indicated. According to the 2021 CCS Dyslipidemia Guidelines, Mr L.P. had a "statin-indicated" condition and should have been started on a statin. Further, after a few months of lifestyle modification with diet, exercise, and weight reduction, his lipid panel was minimally changed, and he was found to have a significantly elevated Lp(a) level. After discussing the risk associated with this level of Lp(a) and his baseline cholesterol values, Mr L.P. was interested in and agreeable to the initiation of a statin to reduce his future risk of ASCVD events.

Over the next few months, alongside ongoing lifestyle modification, he was up-titrated to rosuvastatin 40 mg daily and ezetimibe 10 mg daily. At his last follow-up, his weight was reduced to 88.4 kg, and his BMI had decreased to 27.3 kg/m^2. His repeat lipid panel demonstrated the following measures: TG, 1.82 mmol/L; TC, 2.42 mmol/L; HDL-C, 0.71 mmol/L; LDL-C, 0.88 mmol/L; non-HDL-C, 1.71 mmol/L; and Apo-B, 0.66 g/L. Lp(a) level was not remeasured. At this point, he is optimally controlled, based on the currently available evidence and the 2021 CCS Dyslipidemia Guidelines. In this case, the measurement of a significantly abnormal Lp(a) level was sufficient additional evidence to help facilitate the decision to initiate treatment with lipid-lowering agents for the primary prevention of future ASCVD events.

Figure 2. Case 2: Statin-hesitant primary prevention patient with a statin-indicated condition. ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; CCS, Canadian Cardiovascular Society; DCLN, Dutch Lipid Clinic Network Criteria; ECG, electrocardiogram; FH, familial hypercholesterolemia; FRS, Framingham Risk Score; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein A; LV, left ventricular; PET/CT, positron emission tomography/computed tomography; RBBB, right-bundle branch block; TC, total cholesterol; TG, triglyceride.

isoforms, serum Lp(a) concentrations still varied by up to 200-fold.[61,62] Conversely, studies comparing related patients with the same apo(a) isoforms found serum Lp(a) concentrations to be similar, varying by a maximum of only 2.5-fold.[62] Studies in multiethnic populations also have demonstrated widely different median Lp(a) values among groups, highlighting the need to individualize Lp(a) cutoff values for ASCVD risk assessment.[63]

Lp(a)-lowering therapies

Following screening, risk assessments, and health behaviour counselling, pharmacologic therapies and assessment of intervention efficacy are often the next steps in primary prevention of ASCVD. With its clear link to increased ASCVD risk, Lp(a) appears to be an ideal target for therapy. Currently, however, no available evidence demonstrates that

CASE 3

Mr S.P. is 64-year-old Black man from South Africa who has history of ASCVD, hypothyroidism, hypertension, diabetes, and moderate renal impairment. He experienced an ST-segment MI at the age of 60 years, underwent PCI at the age of 61 years, and received 2 DESs in his left-anterior descending artery. He had a repeat PCI with a DES implanted in his right coronary artery 1 year later. After another admission this year with an acute event, he underwent CABG surgery. You are seeing him in your cardiology follow-up clinic 10 months after his CABG surgery. His current medications include the following: ECASA 81 mg daily, ramipril 10 mg daily, amlodipine 10 mg daily, metformin 1000 mg b.i.d, empagliflozin 10 mg daily, atorvastatin 80 mg, and evolocumab 140 mg subcutaneously every 2 weeks (initiated after his recurrent PCIs and covered by his private insurance drug plan). His pre-clinic bloodwork revealed the following: triglyceride, 1.6 mmol/L; TC, 2.33 mmol/L; HDL-C, 0.9 mmol/L; LDL-C, 0.7 mmol/L; non-HDL-C, 1.43 mmol/L; Apo-B, 0.57 g/L; hemoglobin A1c, 6.4%; TSH, 1.37 mIU/L; serum creatinine, 182 μmol/L (estimated glomerular filtration rate: 34 mL/min per 1.73 m^2); and an Lp(a) of 134 nmol/L. His physical examination is completely normal, with a blood pressure of 127/81 mm Hg.

His Lp(a) level is in the 75th percentile for Black individuals, increasing his lifetime risk for major CV events ~1.5-fold.[19] Given his aggressive lipid treatment with the combination of atorvastatin and evolocumab, his LDL-C control is excellent, at 0.7 mmol/L—well below the threshold for further intensification of ≥ 1.8 mmol/L. Additionally, both his non-HDL-C and Apo-B levels are below the thresholds of ≥ 2.54 mmol/L and ≥ 0.70 g/L, respectively. Although his Lp(a) level is elevated, his CV risk is optimally treated. In the absence of current evidence and available therapies that target lowering of Lp(a) level to improve CV outcomes, no additional recommendation is available to be provided to this patient. He should maintain adherence to his current medication regimen and be followed annually to ensure that all of his CV risks continue to be managed optimally. If in the future, evidence shows that Lp(a)-targeted therapies reduce CV risk, he is a potential candidate for one of these agents.

Figure 3. Case 3: Secondary prevention patient. ApoB, apolipoprotein B; ASCVD, atherosclerotic cardiovascular disease; b.i.d., twice a day; CABG, coronary artery bypass graft; CV, cardiovascular; DES, drug-eluting stent; ECASA, enteric coated acetylsalicylic acid; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein a; MI, myocardial infarction; PCI, percutaneous coronary intervention; TC, total cholesterol; TSH, thyroid-stimulating hormone.

lowering Lp(a) levels decreases the overall risk of cardiac morbidity and mortality. Also unclear is how much the Lp(a) level needs to be lowered to produce a clinically significant reduction in CV events. Ongoing studies, including the Lp(a)HORIZON trial [Assessing the Impact of Lipoprotein (a) Lowering With Pelacarsen (TQJ230) on Major Cardiovascular Events in Patients With CVD], may provide further insights in the future. Of the currently available lipid-lowering therapies on the market, statins paradoxically have been found to marginally increase Lp(a) levels,[64-67] although continuation of statin therapy to lower LDL-C and apoB-related particles is still recommended, as its overall cardiovascular benefit greatly outweighs any modest increase in Lp(a) concentrations. Ezetimibe, a cholesterol-absorption inhibitor, has no effect on Lp(a) levels.[4] In **F**urther Cardiovascular **Ou**tcomes **R**esearch With PCSK9 **I**nhibition in Subjects With **E**levated **R**isk (FOURIER) and the Study to Evaluate the Effect of Alirocumab on the Occurrence of Cardiovascular Events in Patients Who Have Experienced an Acute Coronary Syndrome (ODYSSEY OUTCOMES), proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, which target a pathway promoting LDL-C synthesis, were shown to have greater absolute ASCVD risk reduction in populations with higher baseline Lp(a) levels, and to actually reduce Lp(a) by 15%-20% in individuals in the top quartile of Lp(a) concentration. PCSK9 inhibitors, however, are not currently indicated for Lp(a) management.[19] Niacin has been found to lower Lp(a) concentrations, but it is not recommended, given its toxicities and lack of clear clinical benefits in the statin era.[2,68] Lipoprotein apheresis is another possible Lp(a)-lowering therapy, although it is not easily accessible, is expensive, with only transient effects, comes with associated procedural risks, and has no proven benefit for ASCVD outcomes.

Antisense oligonucleotides and small interfering RNA (siRNA) are novel dyslipidemia therapies on the horizon. Inclisiran, recently approved by Health Canada, the US Food and Drug Administration, and the European Medicines Agency for treatment of hypercholesterolemia, is an siRNA against PCSK9.[69] Compared with PCSK9 inhibitors, which target already synthesized serum PCSK9, inclisiran works upstream to decrease PCSK9 production within the liver. Through inclisiran's chemical conjugation with triantennary N-Acetylgalactosamine, a ligand that binds specifically to asialoglycoprotein receptors expressed by hepatocytes, inclisiran is selectively distributed to the liver. There it binds to and degrades PCSK9 mRNA within the cytoplasm of hepatocytes, ultimately increasing binding of circulating LDL to the LDL-receptors, with subsequent decrease in serum LDL-C.[70,71] Studies to date have shown both a significant and prolonged LDL-C–lowering effect with inclisiran use, which has the added benefit of needing only biannual administration.

Pelacarsen and olpasiran, 2 emerging therapies targeting apo(a) synthesis, have shown promise in targeting Lp(a) levels. Pelacarsen, an antisense oligonucleotide, is designed to target apo(a) mRNA in hepatocytes. Upon binding to apo(a)

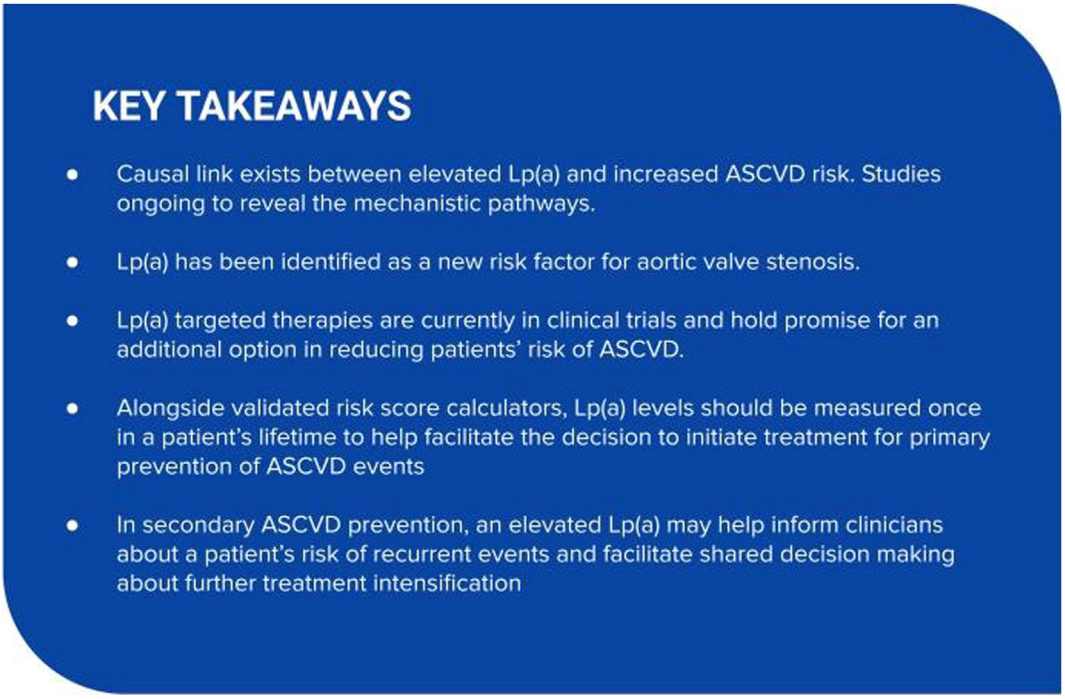

Figure 4. Key takeaways. ASCVD, atherosclerotic cardiovascular disease; Lp(a), lipoprotein a.

mRNA in both the cytoplasm and nucleus, pelacarsen silences the gene and signals for the degradation of the apo(a) mRNA molecule. Olpasiran, an siRNA, works in a similar fashion to selectively bind apo(a) mRNA mainly in the cytoplasm, thus preventing downstream synthesis of apo(a) and Lp(a). In recent studies, pelacarsen was shown to significantly lower Lp(a) and mildly reduce LDL-C levels.[72,73] Olpasiran significantly reduced Lp(a) concentrations in patients with established ASCVD,[74] an effect that an additional study found to be sustained over 6 months (Table 1). Further, siRNAs are under early development. Oral agents that reduce Lp(a), such as muvalaplin, also are being investigated currently.[75]

Future Directions and Conclusion

The imminent establishment of a definitive causal link between an elevated Lp(a) level and increased ASCVD risk, as well as our growing understanding of lipid metabolism, carries promise for future targeted therapy to reduce our patients' risks of ASCVD events. Cascade testing for elevated Lp(a) level from affected probands with phenotypic dyslipidemia would be an effective approach to identify new cases of high Lp(a) level in families and facilitate earlier and more-intensive health-behaviour modification counselling and management of other ASCVD risk factors in primary prevention patients. Research specifically on lowering Lp(a) levels and its effects on MACE reduction is ongoing and highlights exciting possibilities in the field of preventive cardiology. Until such new evidence is available, clinicians are encouraged to measure an Lp(a) level once in a patient's lifetime and utilize this factor, when elevated, to further inform a patient's individualized ASCVD risk and treatment decision-making for primary prevention. In primary prevention, important steps in interacting with patients are to maintain perspective on elevated Lp(a) level, to not unduly alarm the patient, and to emphasize that efforts to improve modifiable risk factors will effectively reduce ASCVD risk. In secondary prevention, an elevated Lp(a) level may help inform clinicians regarding both the risk of recurrent ASCVD events in patients, and decision-making about treatment intensification beyond maximum-tolerated statin doses. We provide three case examples (Figs. 1-3) to demonstrate the utility and potential application of a patient's Lp(a) level in the assessment and treatment of adults at risk for ASCVD. Key takeaways of this review are available in Figure 4.

Ethics Statement

This is a review article and the cases presented are purely fictional. No ethics approval is required for such a manuscript.

Patient Consent

The authors confirm that patient consent is not applicable to this article. The authors invented the cases to specifically highlight to readers the application of Lp(a) measurement in the risk assessment of ASCVD in adult patients.

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