Lipoprotein (a) in Cardiovascular Risk Assessment and Management in Diabetes Mellitus

Gordon A. Francis, MDCM, FRCPC, FAHA

About the Author

Dr. Gordon Francis joined the Division of Endocrinology and Metabolism and Department of Medicine at the University of British Columbia in 2007 as a professor. He is an investigator in the Centre for Heart Lung Innovation and Providence Health Care Research Institute, and from 2007 to 2020, was director of the Prevention Clinic, both based at St. Paul's Hospital. His laboratory has done pioneering research showing the major role of cholesterol build up in artery smooth muscle cells in the development of atherosclerosis, the cause of most heart attacks and strokes. His laboratory is also studying the role of smooth muscle cells in development of cerebral amyloid angiopathy in Alzheimer's and other forms of dementia. Dr. Francis completed a BSc in Biochemistry at Simon Fraser University, medical school at McGill University, internal medicine and endocrinology residencies at the University of British Columbia and University of Alberta, and a senior research fellowship at the University of Washington. In addition to research and clinical work, he is involved in the development of national guidelines for the diagnosis and management of lipid abnormalities to prevent cardiovascular disease.

Affiliations

Department of Medicine, Centre for Heart Lung Innovation, Providence Research, St. Paul's Hospital, University of British Columbia

Introduction

Lipoprotein (a) [Lp(a)] is an independent and genetically-determined risk factor for coronary heart disease (CHD) and stroke that is not changed by alterations in lifestyle factors. It is now recommended by Canadian and other national lipid guidelines to be measured once in a person's lifetime as part of overall assessment for cardiovascular risk, along with family history; presence of hypercholesterolemia; Type 2 diabetes (T2DM); hypertension; and smoking. The presence of elevated Lp(a) confers additional risk to the already high cardiovascular risk in individuals with T2DM. This review summarizes the nature and association of Lp(a) with elevated cardiovascular disease (CVD) risk; the increased cardiovascular risk in individuals with T2DM; potential therapies to lower Lp(a); whether or not to measure Lp(a); and recommendations on how to respond to the finding of elevated Lp(a) in a patient with T2DM.

Lp(a): Definition and Importance

Lp(a) is a lipoprotein molecule that is not reported along with the standard lipid profile. It consists of an LDL-like particle with an additional protein, apolipoprotein(a) [apo(a)] bound to apolipoprotein B of LDL by a disulfide bond (**Figure 1**).

Genetic variants in the LPA locus that regulate Lp(a) levels have been shown by Mendelian randomization studies to clearly associate with CHD risk, thereby strongly suggesting a causal association between Lp(a) and CVD.[1,2] Increased CVD risk with elevated Lp(a) is independent of the low density lipoprotein cholesterol (LDL-C) level and other major CVD risk factors,[3] and is thought to increase CVD risk by mechanisms including increased atherogenesis, inflammation and thrombosis.[4] Levels of Lp(a) >500 mg/L (>100 nmol/L) are found in approximately 20% of individuals of European and South Asian descent, 40% of African American individuals, and 10% of East Asian

doi.org/10.58931/cdet.2023.1315

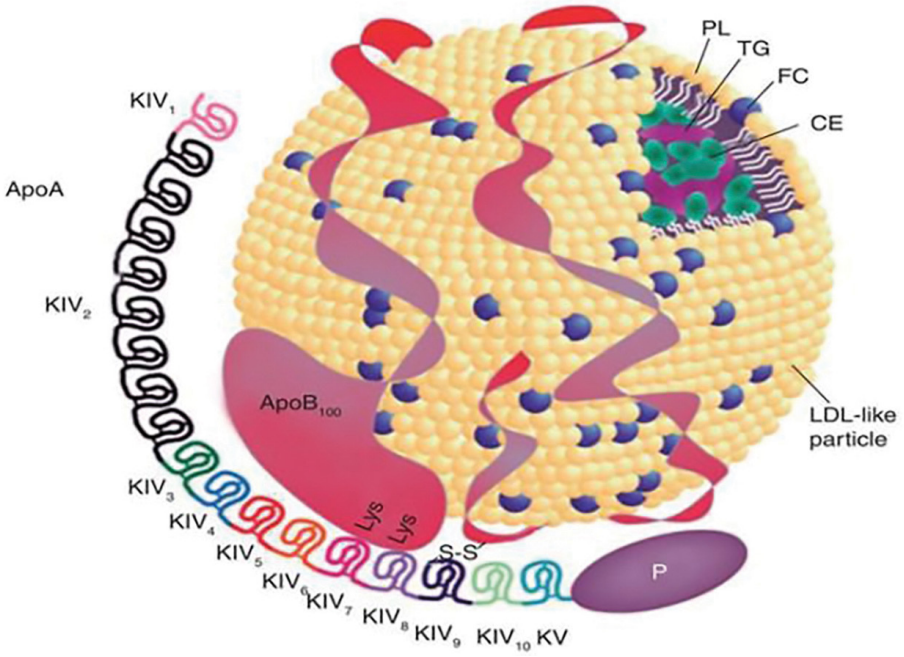

Figure 1. Lipoprotein (a); *courtesy of Gordon A. Francis, MD.*

individuals.[5,6] High Lp(a) is thus an extremely common CVD risk factor. Levels of Lp(a) are almost entirely genetically determined, (i.e., do not significantly vary by by changes in lifestyle including diet, exercise and weight change, and are not lowered by the use of standard lipid medications such as statins or ezetimibe.) *As a result, Lp(a) can be measured once in a person's lifetime, and does not need to be repeated* unless the individual is taking agents such as PCSK9 inhibitors or in the case of expected upcoming therapies that are capable of lowering Lp(a), as described below.

Based on the very strong correlation of Lp(a) level with CVD risk independent of other major coronary risk factors, and the standardization of Lp(a) clinical assays, since 2019 in the European Atherosclerosis Guidelines and since 2021 in the Canadian Lipid Guidelines, it has been recommended that all adults have Lp(a) measured once in their lifetime as part of routine cardiovascular risk assessment.[7,8] Measurement of Lp(a) can take place when an individual has their lipid profile measured for the first time in their lives,[8] or at any time thereafter.

Consideration that Lp(a) may be the reason for premature vascular events or a contributor to recurrent vascular events should be given when a patient suffers a premature coronary event or stroke in the absence of other obvious risk factors such as hypercholesterolemia, smoking, diabetes, or hypertension, or when a secondary prevention patient has recurrent events despite otherwise good control of background risk factors including achievement of recommended LDL-C targets. In such cases, elevated Lp(a) is very frequently the explanation for a patient's premature or recurrent vascular event.

Increased Cardiovascular Risk in T2DM with Elevated Lp(a)

The presence of T2DM confers markedly increased risk of cardiovascular disease even in the absence of elevated Lp(a). Men and women with T2DM have the same cardiovascular risk at age 45 as individuals without T2DM at age 70, demonstrating the profound effect diabetes has on cardiovascular age.[9] The reasons for such high cardiovascular risk in T2DM are not fully understood. However, they comprise dyslipidemia including the presence of small, dense LDL and increased remnant lipoprotein cholesterol due to impaired lipoprotein metabolism, chronic inflammation, hypercoagulability, and the effects of hyperglycemia on endothelial cell and other cell functions.[10,11]

Elevated Lp(a) has been shown to increase CVD risk in individuals with T2DM to a greater extent than in those without the disease, and to increase risk to a greater extent in individuals with T2DM vs those with T2DM and normal Lp(a).[12] The presence of CVD was found to be increased in individuals with T2DM and elevated Lp(a) vs those with T2DM and no Lp(a) elevation with an odds ratio for coronary artery disease (CAD) of 1.6.[13] Data from the Biomarkers for Cardiovascular Risk Assessment in Europe (BiomarCaRE) study found the highest Lp(a)-associated CVD risk in individuals with T2DM compared to those without T2DM (HR for major coronary events 1.31 and for CVD 1.22 with T2DM vs 1.15 and 1.13 without T2DM, respectively).[14] Another multicentre study compared individuals with prediabetes or T2DM to individuals with normal glucose metabolism. The results showed that with Lp(a) >500 mg/dL (100 nmol/L), prediabetes conferred a 2.7-fold increased risk and T2DM a 3.5-fold increase in cardiovascular events vs individuals with normal glucose and the same level of elevated Lp(a).[15] The Atherosclerosis Risk in Communities (ARIC) Study with 15-year follow-up found that with

Lp(a) >500 mg/dl, risk of an incident CVD event was increased in the presence of prediabetes (HR 1.35) or T2DM (HR 1.42) vs individuals with normal fasting glucose.[16] The combined evidence indicates that elevated Lp(a) is a major risk enhancer for CVD in individuals with prediabetes or T2DM. At this time, the relationship of elevated Lp(a) with CVD risk in individuals with T1DM is less clear.[12]

In addition to increasing macrovascular risk in T2DM, elevated Lp(a) is also associated with a higher risk of microvascular complications including neuropathy and nephropathy, indicating that high Lp(a) is a general biomarker of increased risk of complications in T2DM.[17]

Novel Therapies to Lower Lp(a)

Improvement in lifestyle measures or T2DM control do not lower Lp(a), nor do T2DM medications or commonly-used lipid-lowering medications including statins or ezetimibe. The PCSK9 inhibitors evolocumab and alirocumab can reduce Lp(a) levels up to 25%. The reduction in cardiovascular outcomes with PCKS9 inhibitors may be related, in part, to their ability to lower Lp(a), independent of lowering of LDL-C.[18,19] Novel agents that can lower Lp(a) very effectively, including antisense oligonucleotides and those that silence RNA against apo(a), are currently being tested in robust cardiovascular outcome trials to determine the additional benefit of lowering Lp(a) on a background of effective LDL-C-lowering therapy. These trials are expected to report outcomes in the next 3–4 years.[20] These trials are expected to have large cohorts of patients with T2DM to allow subanalysis of these agents' benefits in T2DM. The elevated CVD risk conferred by elevated Lp(a) in T2DM suggests that individuals with T2DM could potentially benefit proportionally more from these agents than individuals with elevated Lp(a) but without T2DM.

It has been estimated that the amount of Lp(a) lowering required to achieve the same cardiovascular benefit as lowering LDL-C by 1 mmol/L is ~1000 mg/L or 214 nmol/L.[21] That suggests that if Lp(a)-lowering treatments are shown to add to the cardiovascular protection achieved with current LDL-lowering therapies, those individuals with the highest baseline Lp(a) levels will be the most likely to benefit. Several reports have found an association between very low levels of Lp(a) and increased risk of developing T2DM (summarized in Ward et al).[12] Whether there could be increased risk of developing T2DM with the use of Lp(a)-lowering drugs remains to be determined from ongoing clinical trials.

Should Lp(a) be Measured in Patients with T2DM?

Canadian and other international guidelines for the assessment and management of dyslipidemia now recommend measuring an individual's Lp(a) level once in a lifetime as part of overall cardiovascular risk assessment. The Canadian lipid guidelines recommend measuring Lp(a) at the same time as the first lipid profile measurement.[8] It is recommended that all individuals have Lp(a) measured even in the absence yet of agents that lower Lp(a) very effectively, to identify those at highest risk, and to reduce other modifiable risk factors as much as possible. While this guideline has been in place for two years, it is anticipated that it will take considerable time for general practitioners and specialists to become more aware of the risk of elevated Lp(a) and the need to measure it routinely. Attendance at a consultation for T2DM or at a specialty diabetes clinic provides an opportunity for Lp(a) measurement to be instituted as a routine policy, if it has not already been measured, given that it may not be measured in other settings.

Course of Action for Elevated Lp(a)

The current approach to finding elevated Lp(a) is to do a thorough review of all other major risk factors (hypercholesterolemia; smoking; T2DM; hypertension; family history of premature coronary disease or stroke), work to control the modifiable factors, and possibly performing vascular imaging such as carotid ultrasound or coronary calcium score to identify plaque. A shared decision-making process with the patient regarding whether or not to institute statin therapy should then occur based on all these factors. Statins have been shown to significantly reduce the CVD risk associated with elevated Lp(a), even though they do not lower Lp(a).[22] Given the significantly worse CVD and microvascular outcomes in people with T2DM who also have high Lp(a), a finding of elevated Lp(a) in a patient with T2DM should stress the need to institute effective statin +/− other LDL-C-lowering therapy possibly sooner than current recommendations regarding the timing of statin initiation in diabetes (T2DM or T1DM over age 40, or over age 30 with more than 15 years of diabetes, or the presence of any microvascular complications).[8] Although PCSK9 inhibitors can lower Lp(a) by up to 25%, elevated Lp(a) in the absence or presence of T2DM is not yet a provincially-funded indication for PCSK9 inhibitors unless the patient also has familial

hypercholesterolemia. Patients with documented symptomatic or subclinical ischemic vascular disease and with or without T2DM who do not achieve recommended lipid targets despite maximally-tolerated statin therapy plus ezetimibe may qualify for PCSK9 inhibitor treatment if they carry private insurance.

Lipid targets for all individuals with the statin-indicated definition of diabetes are LDL-C <2.0 mmol/L, nonHDL-C <2.6 mmol/L, and apoB <0.8 g/L. In the presence of any known cardiovascular disease, including subclinical disease found on a vascular imaging study, or in the presence of Lp(a) >100 nmol/L (500 mg/L), the lipid targets should be LDL-C <1.8 mmol/L, non-HDL-C <2.4 mmol/L, or apoB <0.7 g/L. In patients with T2DM who are resistant to taking statin therapy, the additional finding of elevated Lp(a), which will be present in approximately 20% of patients with T2DM as in the general population, provides another opportunity and rationale to convey the huge benefit of initiating lipid-lowering therapy in T2DM.

Conclusion

Lp(a) is a genetically determined factor known to be elevated in ~20% of the population including patients with T2DM. It is a major risk enhancer for cardiovascular disease, including adding significantly to the already high cardiovascular risk associated with T2DM. Lp(a) is recommended to be measured once in a lifetime as an integral part of overall CVD risk assessment. An office or specialty diabetes clinic consultation represents an excellent opportunity to screen for elevated Lp(a) if it has not yet been performed, and to further tailor cardiovascular disease preventive measures for patients with T2DM.

Correspondence

Dr. Gordon Francis
Email: gordon.francis@hli.ubc.ca

Financial Disclosures

None declared.

References

1. Clarke R, Peden JF, Hopewell JC, et al. Genetic variants associated with Lp(a) lipoprotein level and coronary disease. N Engl J Med. 2009 Dec 24;361(26):2518–2528.
2. Kamstrup PR, Tybjaerg-Hansen A, Steffensen R, et al. Genetically elevated lipoprotein(a) and increased risk of myocardial infarction. JAMA. 2009 Jun 10;301(22):2331–2339.
3. Nordestgaard BG, Chapman MJ, Ray K, et al. Lipoprotein(a) as a cardiovascular risk factor: current status. Eur Heart J. 2010 Dec;31(23):2844–2853.
4. Reyes-Soffer G, Ginsberg HN, Berglund L, et al. Lipoprotein(a): a genetically determined, causal, and prevalent risk factor for atherosclerotic cardiovascular disease: a scientific statement from the American Heart Association. Arterioscler Thromb Vasc Biol. 2022 Jan;42(1):e48–60.
5. Paré G, Çaku A, McQueen M, et al. Lipoprotein(a) levels and the risk of myocardial infarction among 7 ethnic groups. Circulation. 2019 Mar 19;139(12):1472–1482.
6. Enkhmaa B, Anuurad E, Berglund L. Lipoprotein (a): impact by ethnicity and environmental and medical conditions. J Lipid Res. 2016;57(7):1111–1125.
7. Mach F, Baigent C, Catapano AL, et al. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. Eur Heart J. 2020 Jan 1;41(1):111–188.
8. Pearson GJ, Thanassoulis G, Anderson TJ, et al. 2021 Canadian Cardiovascular Society Guidelines for the Management of Dyslipidemia for the Prevention of Cardiovascular Disease in Adults. Can J Cardiol. 2021 Aug;37(8):1129–1150.
9. Booth GL, Kapral MK, Fung K, et al. Relation between age and cardiovascular disease in men and women with diabetes compared with non-diabetic people: a population-based retrospective cohort study. Lancet. 2006 Jul 1;368(9529):29-36.
10. Low Wang CC, Hess CN, Hiatt WR. Clinical update: cardiovascular disease in diabetes mellitus: atherosclerotic cardiovascular disease and heart failure in type 2 diabetes mellitus - mechanisms, management, and clinical considerations. Circulation. 2016 Jun 14;133(24):2459–2502.
11. Bornfeldt KE. The remnant lipoprotein hypothesis of diabetes-associated cardiovascular disease. Arterioscler Thromb Vasc Biol. 2022 Jul;42(7):819-830.
12. Ward NC, Vickneswaran S, Watts GF. Lipoprotein (a) and diabetes mellitus: causes and consequences. Curr Opin Endocrinol Diabetes Obes. 2021 Apr 1;28(2):181-187.
13. Zhang HW, Zhao X, Guo YL, et al. Elevated lipoprotein (a) levels are associated with the presence and severity of coronary artery disease in patients with type 2 diabetes mellitus. Nutr Metab Cardiovasc Dis NMCD. 2018 Oct;28(10):980-986.
14. Waldeyer C, Makarova N, Zeller T, et al. Lipoprotein(a) and the risk of cardiovascular disease in the European population: results from the BiomarCaRE consortium. Eur Heart J. 2017 Aug 21;38(32):2490-2498.
15. Jin JL, Cao YX, Zhang HW, et al. Lipoprotein(a) and Cardiovascular Outcomes in Patients With Coronary Artery Disease and Prediabetes or Diabetes. Diabetes Care. 2019 Jul;42(7):1312-1318.
16. Saeed A, Sun W, Agarwala A, Virani SS, Nambi V, Coresh J, et al. Lipoprotein(a) levels and risk of cardiovascular disease events in individuals with diabetes mellitus or prediabetes: The Atherosclerosis Risk in Communities study. Atherosclerosis. 2019 Mar;282:52-56.
17. Moosaie F, Davatgari RM, Firouzabadi FD, et al. Lipoprotein(a) and apolipoproteins as predictors for diabetic retinopathy and its severity in adults with type 2 diabetes: a case-cohort study. Can J Diabetes. 2020 Jul;44(5):414-421.
18. O'Donoghue ML, Fazio S, Giugliano RP, et al. Lipoprotein(a), PCSK9 inhibition, and cardiovascular risk. Circulation. 2019;19;139(12):1483-1492.
19. Bittner VA, Szarek M, Aylward PE, et al. Effect of alirocumab on lipoprotein(a) and cardiovascular risk after acute coronary syndrome. J Am Coll Cardiol. 2020 Jan 21;75(2):133-1344.
20. Malick WA, Goonewardena SN, Koenig W, et al. Clinical trial design for lipoprotein(a)-lowering therapies: JACC focus seminar 2/3. J Am Coll Cardiol. 2023 Apr 25;81(16):1633-1645.
21. Burgess S, Ference BA, Staley JR, et al. Association of LPA variants with risk of coronary disease and the implications for lipoprotein(a)-lowering therapies: a Mendelian randomization analysis. JAMA Cardiol. 2018 01;3(7):619-627.
22. Maher VM, Brown BG, Marcovina SM, et al. Effects of lowering elevated LDL cholesterol on the cardiovascular risk of lipoprotein(a). JAMA. 1995 Dec 13;274(22):1771-1774.