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

Gordon A. Francis, MDCM, FRCPC, FAHA

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. Increased CVD risk with elevated Lp(a) is independent of the low density lipoprotein cholesterol (LDL-C) level and other major CVD risk factors, and is thought to increase CVD risk by mechanisms including increased atherogenesis, inflammation and thrombosis. 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
individuals. 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. Measurement of Lp(a) can take place when an individual has their lipid profile measured for the first time in their lives, 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. 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.

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). 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.

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). 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). 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.\(^\text{16}\) 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.\(^\text{12}\)

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.\(^\text{17}\)

**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 PCSK9 inhibitors may be related, in part, to their ability to lower Lp(a), independent of lowering of LDL-C.\(^\text{18,19}\) 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.\(^\text{20}\) 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.\(^\text{21}\) 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).\(^\text{12}\) 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.\(^\text{8}\) It is recommended that all individuals have Lp(a) measured even in the absence 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).\(^\text{22}\) 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).\(^\text{8}\) 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, non-HDL-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.
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