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High levels of lipoprotein(a) – assessment and treatment

CLINICAL REVIEW

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Approximately 5 % of the population have highly elevated levels of lipoprotein(a) (Lp(a)), which is a genetically determined risk factor for cardiovascular disease. Measuring lipoprotein(a) can improve cardiovascular risk stratification and have consequences for preventive measures. Treatment is targeted at reducing modifiable cardiovascular risk factors, but Lp(a)-lowering drugs are being trialled. This article reviews the management of lipoprotein(a) in clinical practice.

Lipoprotein(a), abbreviated as Lp(a) and often referred to as *lipoprotein little a*, was first identified in 1963 by the Norwegian Kåre Berg (1). In recent years, lipoprotein(a) has gained increased attention as a risk factor for cardiovascular disease after several studies demonstrated that cardiovascular risk increases proportionally with increasing levels of lipoprotein(a) (2–9). Treatment for selective reduction of plasma lipoprotein(a) is currently being trialled (10). Lipid clinics in Norway are experiencing ever-increasing volumes of enquiries related to lipoprotein(a). According to reimbursement data from the Norwegian Control and Payment of Health Reimbursements (KUHR) database, approximately 50,000 measurements of lipoprotein(a) were performed in 2021 (Vegard Håvik, personal communication).

The European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS) published guidelines for lipoprotein(a) in 2019 (11). This article aims to give a short review of lipoprotein(a) as a cardiovascular risk factor and to outline strategies for the assessment and treatment of high lipoprotein(a) levels, adapted to the situation in Norway. The article is based on a discretionary selection of the relevant literature, Norwegian and international guidelines, the authors' own clinical experience and a specialist procedure.

Pathophysiology

Lipoprotein(a) is a low-density lipoprotein (LDL) particle with an added apolipoprotein, apolipoprotein(a) (abbreviated as apo(a)). Apolipoprotein(a) contains loop structures called kringles. Apolipoprotein(a) size is determined

by the number of copies of kringle IV type 2 (KIV type 2) and is inversely correlated with levels of Lp(a) (Figure 1). The number of copies is determined by variations in the gene encoding apolipoprotein(a) (the LPA gene).

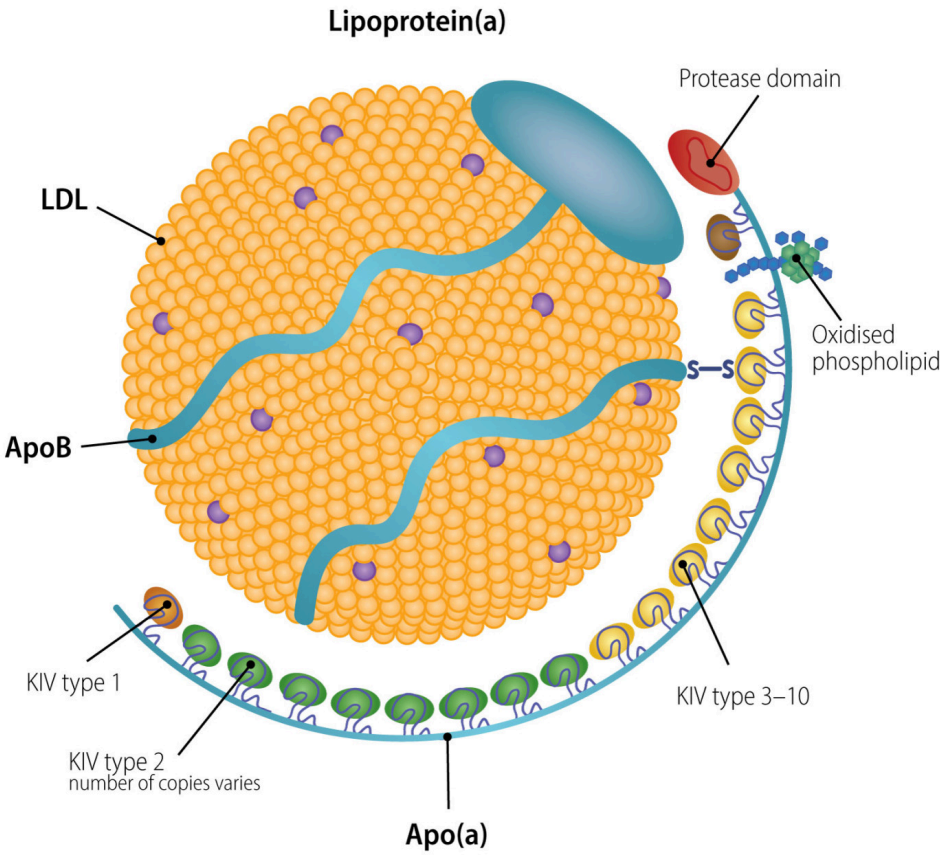

Figure 1 The structure of lipoprotein(a). Lipoprotein(a) is an LDL particle attached to apolipoprotein(a) (apo(a)). Apolipoprotein(a) consists of loop-like structures called *kringles*. Apolipoprotein(a) size is determined by the number of copies of *kringle IV type 2* (KIV type 2) and is inversely correlated with levels of lipoprotein(a). The figure shows eight copies of KIV type 2. Apolipoprotein(a) can bind oxidised phospholipids. ApoB = apolipoprotein B. Illustration: Illumedic

Lipoprotein(a) is thought to cause atherosclerosis as a result of both its cholesterol-rich LDL particle and apolipoprotein(a). The LDL particle can penetrate through the endothelial wall and cause lipid deposition, and apolipoprotein(a) can bind oxidised phospholipids and induce an inflammatory response, which in turn can lead to atherosclerosis and aortic valve calcification (7). Apolipoprotein(a) structurally resembles plasminogen and, in theory, may influence coagulation (12).

Incidence

Levels of lipoprotein(a) are primarily determined by genetic factors, remain very stable throughout life and are relatively unaffected by dietary habits and lifestyle. The distribution of Lp(a) levels in the population is skewed: about 20 % have elevated levels exceeding approximately 125 nmol/L (approximately 500 mg/L) (2, 3, 11, 13). The population data are mainly based on European

populations. Individuals of African and Asian descent are known to have higher and lower Lp(a) levels respectively (9, 14). However, no difference in increased cardiovascular risk for an equal Lp(a) increment was found in various ethnic groups (14). No relevant differences have been detected between sexes in thresholds or Lp(a)-associated risk (3).

Diagnostic testing

Elevated levels of lipoprotein(a) do not themselves cause clinical symptoms. Isolated elevated Lp(a) levels are rarely treated alone. Therefore, national expert guidelines for cardiovascular disease prevention advise against routine measurement of lipoprotein(a) (15). European guidelines from 2019 allow for measurement of lipoprotein(a), even without other risk factors, in order to identify individuals with exceptionally high levels (11). This is partly based on the results of a large mendelian randomisation analysis which demonstrated that very high levels (above 430 nmol/L) can result in a three/four-fold increase in the risk of coronary heart disease, a risk similar to familial hypercholesterolaemia (8).

Measurement of Lp(a) can improve risk stratification and have consequences for future diagnostic assessment and optimisation of preventive treatment. At Oslo University Hospital, we have developed a specialist procedure with recommendations for the assessment of Lp(a) levels (16). Measuring Lp(a) levels should be considered once in a lifetime as part of the lipid profile in cardiovascular risk assessment (2–4, 8, 14, 17) and particularly in the conditions described in Box 1 (7, 13).

Box 1 Conditions in which lipoprotein(a) may be a particular risk-modulating factor. Based on Nordestgaard et al. (7) and Wilson et al. (13).

Intermediate cardiovascular risk where additional information about Lp(a) levels takes the patient over the intervention threshold. Age-dependent intervention threshold in NORRISK 2 (45–54 years: > 5 %, 55–64 years: > 10 %, 65–74 years: > 15 %) (20).

Family history of premature cardiovascular disease

Severe elevation of LDL cholesterol or familial hypercholesterolaemia

Premature cardiovascular disease

Recurrent cardiovascular disease with control of other cardiovascular risk factors

Blood sample analysis

Lipoprotein(a) is measured in nmol/L or mg/L. There are inaccuracies in a conversion factor between the units for reasons that include the analysis method and size of apolipoprotein(a) (18). The conversion factor from mg/L to

nmol/L is approximately 0.24. Conversions for some Lp(a) values are given as a guide in Table 1. Fasting prior to measurement is not required.

Table 1

Population percentiles and cardiovascular risk for various Lp(a) categories, with recommendations for intervention. The conversion factor from mg/L to nmol/L is approximately 0.24. The multiplication factor estimates the increased risk associated with the Lp(a) category in addition to the baseline risk from NORRISK 2 (15).

Degree of Lp(a) elevation	Lp(a) levels (nmol/L)	Lp(a) levels (mg/L)	Percentile of the population	Multiplication factor for cardiovascular risk	Consideration of intervention[1]
Mild	75–125	300–500	75	–	–
Moderate	125–250	500–1,000	80–95	1.5	Yes, for patients with comorbid conditions[2]
High	250–400	1,000–1,800	95–99	1.5[3]	Yes, for patients with comorbid conditions
Very high	> 400	> 1,800	> 99	4	Yes, even without comorbid conditions

[1]Intervention = drug treatment alongside lifestyle advice.

[2]Comorbid conditions as described in Box 1.

[3]Risk increases gradually between the categories (2, 3, 6).

[4]Very high Lp(a) levels can result in as much as a three/four-fold increase in cardiovascular risk, which may itself be grounds for intervention (8, 14, 21).

Lipoprotein(a) contains LDL cholesterol in varying amounts. Therefore, high Lp(a) levels can increase levels of LDL cholesterol in the blood. Statin treatment does not reduce lipoprotein(a) levels and, therefore, will not reduce LDL cholesterol bound to lipoprotein(a) either. This can manifest as resistance to statin treatment (19).

Cardiovascular risk and consideration of intervention

Norwegian laboratories usually specify Lp(a) elevation when levels exceed 75 nmol/L and 300 mg/L. In line with international consensus statements, we use a threshold for increased cardiovascular risk at Lp(a) levels of approximately

125 nmol/L (approximately 500 mg/L) (3, 7, 13). There is no definite increased risk at levels below this threshold. Based on the available literature, Table 1 shows Lp(a) levels according to clinically relevant cardiovascular risk (2, 3, 6).

For an individual assessment of risk associated with elevated Lp(a) levels in primary prevention, the Norwegian national expert guidelines for cardiovascular disease prevention recommend calculating cardiovascular risk using the NORRISK 2 calculator (20) and then revising the estimate upwards by a factor of 1.5 (15), which is the multiplication factor indicated in Table 1. From high to very high Lp(a) levels, this factor is probably on the low side – a two/three-fold increase in the risk of myocardial infarction and aortic valve stenosis has been reported at levels above 250 nmol/L (approximately 1,000 mg/L) (5, 14), and levels above 400 nmol/L (approximately 1800 mg/L) can result in as much as a three/four-fold increase in the risk of ischaemic heart disease (8, 14, 21). Interpretation of borderline levels requires clinical judgement and, in case of uncertainty, referral to the specialist health service. No evidence is available for the use of Lp(a) levels as a risk modulator above the age of 75 years, but the significance is thought to be largely the same.

Intervention

Reduction of total cardiovascular risk

No specific Lp(a)-lowering treatment is currently available (see below). The treatment of individuals with elevated Lp(a) levels is targeted at the other cardiovascular risk factors. It has been demonstrated that patients with a low total risk have a lower cardiovascular risk despite excessively high Lp(a) levels (22).

Treatment follows the Norwegian national expert guidelines for cardiovascular disease prevention (15). This involves focus on dietary and lifestyle measures and, if necessary, treatment of hypertension and diabetes. Most patients will require cholesterol-lowering treatment as well.

The treatment target for LDL cholesterol is assessed on an individual basis. In primary prophylaxis, no specific treatment target has been set for LDL cholesterol in patients with high Lp(a) levels, but the target will often be to reduce LDL cholesterol levels to below 2.5–3 mmol/L in patients at increased risk (11, 13, 20, 22, 23). In patients with conditions entailing a high to very high cardiovascular risk, the target is based on the LDL target given for that condition (for example the LDL target for diabetes, familial hypercholesterolaemia or atherosclerotic disease) (15, 17, 23).

Reduction of lipoprotein(a)

It is likely that levels of lipoprotein(a) will need to be considerably reduced to achieve an effect on cardiovascular events. Theoretical calculations estimate that a reduction in Lp(a) levels of around 100 nmol/L produces almost the same risk reduction as a reduction in LDL cholesterol of 1 mmol/L (8, 17). Post-hoc analyses of studies with PCSK9 (proprotein convertase subtilisin/kexin type 9) inhibitors in secondary prevention report a reduction in Lp(a) levels of

approximately 25 %, but a reduction in cardiovascular events has not been established (24). Selective Lp(a) reduction as primary prevention has not yet been studied.

Lipoprotein apheresis is a dialysis-like treatment that reduces levels of lipoprotein(a) and LDL cholesterol by around 30 % on average. Observational studies have shown a clear reduction in cardiovascular events with lipoprotein apheresis, but it is unclear how much of the effect is due to reduction of lipoprotein(a) and LDL cholesterol respectively (25). The treatment is time-consuming and expensive, but can be considered in cases of very high levels of lipoprotein(a) and recurrent cardiovascular disease despite good control of LDL cholesterol. In Norway, very few patients are treated with lipoprotein apheresis for high Lp(a) levels.

Selective reduction of lipoprotein(a) with drugs such as an apo(a) antisense oligonucleotide is being trialled. This treatment has resulted in a dose-dependent reduction in lipoprotein(a) of 35–80 %, (26). Studies into the effect of Lp(a) reduction on cardiovascular events are expected in 2024 (10). Lp(a)-lowering treatment may then become appropriate adjuvant treatment.

Follow-up

Most Lp(a) measurements will be performed by general practitioners as part of a standard cardiovascular risk assessment (NORRISK 2). Patients are followed up in line with the Norwegian national expert guidelines for cardiovascular disease prevention (15). Follow-up of patients with very high lipoprotein(a) levels in the specialist health service may be indicated.

In the event of possible cardiovascular symptoms or suspected aortic valve disease, the patient should be referred for assessment by a cardiologist or other relevant vascular evaluation.

Children and adolescents

There is limited information about recommendations regarding Lp(a) measurement in children and adolescents below the age of 18 years. Measurements can be performed in the specialist health service when children are considered for lipid-lowering treatment, such as in cases of familial hypercholesterolaemia (13, 27).

Screening of relatives

Due to the heritability of Lp(a), family members of an individual with elevated lipoprotein(a) may also have high levels. However, the significance of the levels and recommended treatment depend on the individual's other risk factors. A risk assessment, including Lp(a) measurement, is recommended in cases of a

first-degree relative having very high Lp(a) levels and premature heart disease themselves or in the immediate family, which is presumed to be due to lipoprotein(a) (13, 16). This also applies to children aged 8 - 10 years, and in these cases the assessment will be primarily a specialist service (27).

Conclusion

Lipoprotein(a) is a fatty substance, and blood levels are genetically determined. High levels are associated with an increased risk of cardiovascular disease. Information about lipoprotein(a) can improve cardiovascular risk stratification and be of relevance for intensification of preventive treatment.

After the manuscript for this article was accepted, a new consensus statement was published in 2022 by the European Atherosclerosis Society (EAS) with a more proactive approach as regards the assessment and treatment of high Lp(a) levels (). Discussions are ongoing about adapting this statement to the situation in Norway. In European and other international guidelines, there is agreement that Lp(a) levels should be interpreted and treated in relation to other cardiovascular risk factors. This implies that lipoprotein(a) should not be measured in isolation without undertaking an assessment of total cardiovascular risk or other comorbid conditions as described in Box 1.

The article has been peer-reviewed.

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