Clinical Guideline

MANAGEMENT OF LIPOPROTEIN (a)

SETTING	Lipid Clinic, University Hospitals Bristol and Weston NHS Foundation Trust
FOR STAFF	Clinical Lipid Clinic Staff
PATIENTS	Adults under the care of the Lipid Clinic team

Introduction

Lipoprotein (a) [Lp(a)] is a modified low-density lipoprotein (LDL) particle, that is atherogenic and a powerful independent cardiovascular disease (CVD) risk factor. It is also a risk factor for calcific aortic stenosis. A wide range of concentrations are found in the general population. Concentration is largely genetically determined, with autosomal co-dominant inheritance, although a small number of secondary causes may affect Lp(a) levels. Concentrations are stable during life unless specific treatment is given or secondary causes are corrected.

Specific Lp(a) lowering treatments are not yet routinely available, but there is evidence that intensive management of dyslipidaemia and other CVD risk factors partially mitigates the Lp(a) associated risk, and this is currently the mainstay of management of patients with high Lp(a) levels. Apheresis may be of benefit in some patients but is not routinely available. PCSK9 inhibitors may reduce Lp(a) by 20-30% but this may not directly confer reduction of CVD risk and they are not currently licensed for treatment of Lp(a) (1). Novel agents targeting Lp(a) synthesis are in development (2).

In whom should Lp(a) be measured?

Lp(a) should be measured at least once in all adults referred to the lipid clinic, preferably in the first lipid profile so as to identify those with high cardiovascular risk (3). Lp(a) should only be measured once and there is no indication for repeating unless secondary causes are identified and corrected. Possible secondary causes of increased Lp(a) include:

- Chronic kidney disease
- Nephrotic syndrome
- Hypothyroidism

Version 2 From: April 2023 to April 2026 Authors: [redacted]

Interpretation of Lp(a)

Table 1: Classification of Lp(a) status based on its impact on CVD risk

Lp(a) (nmol/L)	Population percentile (3)	Impact on CVD risk
<90	<80th	Minor
90 – 200	80th – 95th	Moderate
200 – 400	95th – 99.8th	High
≥400	>99.8th	Very high (CVD risk equivalent to heterozygous familial hypercholesterolaemia)

Reference for percentiles by Kamstrup and colleagues (4).

N.B. Prior to August 2019, Trust Lp(a) results were expressed in mg/dL and this may still be the case for results reported by other laboratories. Precise conversion between mg/dL and nmol/L units is not possible but nmol/L results are approximately 2.4 times higher than those in mg/dL.

Management of patients with raised Lp(a) (>90 nmol/L) *(Adapted from EAS & HEART UK consensus (5,6))*

Lp(a) 90 – 200 nmol/L

- Address all modifiable CVD risk factors, including healthy lifestyle advice (4).
- In patients with a QRISK3 of less than 5%, offer lifestyle advice and suggest a lipid profile and CVD risk assessment in 5 years.
- In patients with a QRISK3 of 5 to 10% offer high intensity statin to treat to primary prevention target, i.e. 40% reduction in non-HDL-cholesterol. This recognises the additional risk factor that raised Lp(a) contributes to CVD risk.
- In patients with a QRISK3 of greater than 10%, treat to secondary prevention target, i.e. LDL-cholesterol less than 1.8 mmol/L (or non-HDL-cholesterol less than 2.5 mmol/L).

Lp(a) ≥200 nmol/L

- Offer high intensity statin and up-titrate or add ezetimibe as necessary.
- If QRISK3 is less than 5%, consider only treating to primary prevention target.
- In all other patients, aim for secondary prevention target.
- Add PCSK9 inhibitor if indicated in accordance with NICE TA393/394/733.
- Recommend Lp(a) testing of first degree relatives and referral to Lipid Clinic if relatives Lp(a) is greater than 400 nmol/L.

Lp(a) ≥400 nmol/L

- Treat to secondary prevention target in all patients.
- As above and consider coronary artery CT angiography

Table 2: Lipid management in primary prevention of CVD in patients with elevated Lp(a)

	10y CVD risk <5%	10y CVD risk 5-10%	10 CVD risk >10%
Lp(a) <90 nmol/L	Lifestyle advice	Lifestyle advice	Treat to primary prevention target
Lp(a) 90-200 nmol/L	Lifestyle advice; risk assessment in five years	Treat to primary prevention target	Treat to secondary prevention target
Lp(a) >200 nmol/L	*Treat to secondary prevention target	Treat to secondary prevention target	Treat to secondary prevention target

** If QRISK3 is less than 5% and Lp(a) 200-400 nmol/L consider only treating to primary prevention target.*

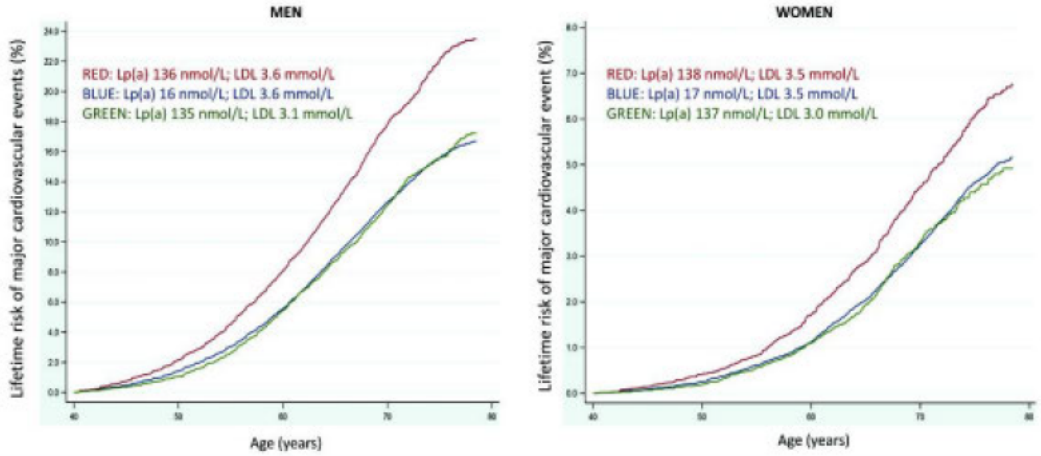
Other issues to be considered for individual patients with raised Lp(a)

- **Calcific aortic valve stenosis.** Elevated Lp(a) is a risk factor for development and progression of calcific aortic valve stenosis (7). General screening with an echocardiogram is not indicated but should be performed in patients with a systolic murmur or symptoms including dyspnoea, angina, syncope and dizziness.
- **Effect of racial origin.** Early studies of Lp(a) and CVD were mainly conducted in Caucasian populations. Lp(a) concentrations may have a greater impact on atherosclerotic plaque progression in Caucasian subjects. Lp(a) concentrations may be up to two times higher in people of black African descent. There are currently no ethnicity specific reference intervals (8).
- **Effect of age.** The risk association between Lp(a) and CVD may be stronger in younger subjects (9).
- **Antithrombotic therapy.** There is currently insufficient evidence of a favourable benefit to risk ratio to support the use of aspirin in primary coronary prevention although this may be considered in patients with imaging evidence of extensive atherosclerosis and minimal bleeding risk (10, 11).
- **Apheresis.** Lipoprotein apheresis can be considered in patients with very high Lp(a) and progressive atherosclerotic CVD despite optimal treatment of other risk factors. (12)
- **Novel agents.** Consider enrolling patients in clinical trials where appropriate.

Figure 1: LDL reduction needed to reduce global cardiovascular risk to a similar extent as the risk attributable to high Lp(a).

Adapted from European Atherosclerosis Society consensus statement (5).

A Lifetime risk of major cardiovascular events with higher lifetime exposure to Lp(a) and lower lifetime exposure to LDL-C



B Intensification of LDL-C reduction needed to reduce the global cardiovascular risk to a similar extent as the risk attributable to elevated Lp(a) depending on age at which LDL-C reduction is initiated

Lp(a) nmol/L	Δ Lp(a) compared to median	Lp(a) percentile	HR for MCVE due to increased Lp(a)	Intensification of LDL-C reduction (nmol/L) needed to mitigate the increased risk caused by Lp(a)			
				Begin age 30y	Begin age 40y	Begin age 50y	Begin age 60 y
320	300	99	2.56	1.2 mmol/L	1.4 mmol/L	1.7 mmol/L	2.3 mmol/L
270	250	97.5	2.19	1.0 mmol/L	1.2 mmol/L	1.5 mmol/L	1.9 mmol/L
220	200	93.5	1.87	0.8 mmol/L	0.9 mmol/L	1.2 mmol/L	1.5 mmol/L
170	150	90	1.60	0.6 mmol/L	0.7 mmol/L	0.9 mmol/L	1.1 mmol/L
120	100	82.5	1.37	0.4 mmol/L	0.5 mmol/L	0.6 mmol/L	0.8 mmol/L
70	50	75	1.17	0.2 mmol/L	0.2 mmol/L	0.3 mmol/L	0.4 mmol/L
20	ref.	50	ref.	ref.	ref.	ref.	ref.

<u>Panel A:</u> Shows cumulative lifetime risk of a major CVS event (defined as myocardial infarction, ischaemic stroke, or coronary revascularization) among 440 368 UK Biobank participants of European descent.
These were split by gender and divided into three groups:

- *reference group with population average Lp(a) [16–17 nmol/L] and LDL [3.5–3.6 mmol/L];*
- *group with Lp(a) [136–138 nmol/L], but with population average LDL [3.5–3.6 mmol/L];*
- *group with Lp(a) [136– 138 nmol/L] BUT lifetime of 0.5 mmol/L lower LDL [3.0-3.1 mmol/L]*

This demonstrates the increased risk of major CVS event caused by approximately 120 nmol/L higher Lp(a) can be mitigated at all ages by a lifetime exposure to approximately 0.5 mmol/L lower LDL.

<u>Panel B:</u> Estimate of the intensification of LDL lowering needed to mitigate the increased risk of major CVS event caused by increasingly higher Lp(a) levels, and the age at which LDL lowering is initiated. Because the proportional reduction in risk produced by LDL decreases with decreasing duration of exposure, greater intensification of LDL lowering is needed to mitigate a given Lp(a) level if LDL lowering is started at a later age. For example, a person with elevated Lp(a) of 220 nmol/L has a 1.87-fold increased risk of major CVS event as compared to if Lp(a) was 20 nmol/L. This increased risk of major CVS event can be mitigated by lowering LDL by 0.8 mmol/L if started at age 30, but would require more intense LDL lowering by 1.5mmol/L if started at age 60.

Appendix – Evidence of Learning from Incidents

The following table sets out any incidents/ cases which informed either the creation of this document or from which changes to the existing version have been made.

Incidents	Summary of Learning
N/A	Guideline produced to ensure best practice as recommended in best practice documents published by the European Atherosclerosis Society and Heart UK (refs 5 and 6)

Table A

REFERENCES

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7. Kamstrup P et al. Elevated Lipoprotein(a) and Risk of Aortic Valve Stenosis in the General Population J Am Coll Cardiol. 2014 Feb 11;63(5):470-
8. Steffen et al. Race-Based Differences in Lipoprotein(a)-Associated Risk of Carotid Atherosclerosis. Arteriosclerosis, Thrombosis, and Vascular Biology. 2019;39:523–529
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11. Gaziano JM et al. Use of aspirin to reduce risk of initial vascular events in patients at moderate risk of cardiovascular disease (ARRIVE): a

	randomised, double-blind, placebo-controlled trial. *Lancet.* 201; 392 (10152): 1036-1046 12. Nugent A, Gray JV, Gorby LK, Moriarty PM. Lipoprotein Apheresis: First FRA Indicated Treatement for Elevated Lipoprotein (a). *Journal of Clinical Cardiology.* 2020: 1, 16-22
RELATED DOCUMENTS AND PAGES	
AUTHORISING BODY	Bristol Lipidologists Meeting.
SAFETY	There are no specific safety concerns beyond those associated with the specific drugs mentioned in this document. Note the caveat that other laboratories may have different units of measurement and therefore produce numerically different results from the Bristol service.
QUERIES AND CONTACT	[redacted].
AUDIT REQUIREMENTS	Audit after one year to include percentage of lipid clinic patients who have had at lease one Lp(a) measurement, and evidence of appropriate management of patients with Lp(a) >90 nmol/L Associated patient information leaflet has been reviewed to ensure that it is are consistent changes to the Guideline in this edition ☒

Plan Elements	**Plan Details**
The Dissemination Lead is:	[redacted]
Is this document: A – replacing the same titled, expired guideline, B – replacing an alternative guideline, C – a new Guideline:	A – replaces version 1 of the same titled guideline
If answer above is B: Alternative documentation this guideline will replace (if applicable):	N/A
This document is to be disseminated to:	Consultants, Drs in Training and GP's with Extended Roles working in UHBW Lipid Clinics
Method of dissemination:	By e-mail
Is training required and how will this be delivered:	No. This document describes best practice already known to the clinical team

Document Change Control

Date of Version	Version Number	Lead for Revisions	Type of Revision	Description of Revision
April 2023	2	[redacted]	Major	Changes in the Lp(a) decision limits for treatment to primary or secondary prevension thresholds, taking into account estimated 10 year cardiovascular risk attributable to other risk factors. Removed requirement for echocardiogram and added recommendation for CT coronary angiogram in patients with very high Lp(a)