

A call to action from the Lipoprotein(a) Taskforce

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Foreword



Jules Payne, Chair of the Lp(a) Taskforce



Henry Smith MP. Parliamentary Sponsor

Lipoprotein(a) - also known as 'lipoprotein little a' or Lp(a) - is one of many risk factors which contribute to the significant burden of cardiovascular disease (CVD) on the NHS and wider society. There are an estimated 7.5 million people living with CVD in the UK, with this figure set to increase in the coming years in line with a growing elderly population, the prevalence of risk factors, and the impact of the Covid-19 backlog.¹

In this context, the newly established Lp(a) Taskforce has come together to support the UK's ambition to become a world-leader in CVD prevention and care. As part of measures introduced to meet this target, it is vital that consideration is given to initiatives that can help to reduce the overall burden of CVD across the country. both on local systems and on patients, including those that can support improved identification and management of atherosclerotic cardiovascular disease (ASCVD) risk factors such as Lp(a). Lp(a) has been the subject of growing academic and clinical interest in recent years as many have realised its potential role in transforming existing approaches to CVD prevention and care. It is therefore vital that steps are taken now to help realise this potential and remove the barriers to the widespread recognition and acceptance of Lp(a) screening across the NHS.

We urge policymakers to consider the Lp(a) Taskforce's calls to action, which have been endorsed by leading experts in the cardiovascular, lipid, and laboratory community in the UK.

Calls to action

The Lp(a) Taskforce is calling for action in the following three main areas. The Taskforce ascribes equal importance to the calls to action and believe that they can be implemented in parallel and independently of one another.

Standardisation of Lp(a) screening and measurement





In the short-term, there is a need to introduce greater standardisation in the screening and measurement of Lp(a). This is particularly important in light of the growing evidence and recognition for Lp(a) as an independent, inherited, and causal risk factor for ASCVD, as demand for Lp(a) screening is anticipated to increase significantly in the coming years.

As such, it is important to ensure that stakeholders work together to address current variation in the screening and measurement of Lp(a), to avoid future challenges as testing becomes more widely adopted in clinical practice.

Including Lp(a) within CVD risk calculators

Including Lp(a) within the Joint British Societies recommendations on the prevention of Cardiovascular Disease (JBS) and QRISK has the potential to improve the accuracy of CVD risk assessments, particularly for patients who are at intermediate risk and have exhibited several clinical predictors of adverse cardiovascular events.^{2,3,4}

The Lp(a) Taskforce is therefore calling for the inclusion of Lp(a) within future updates to the criteria of both risk calculators to inform improved risk factor management.⁵

Including Lp(a) within clinical guidelines

The Taskforce is also calling for the inclusion of specific recommendations for Lp(a) within the next update to the National Institute for Health and Care Excellence (NICE) clinical guideline on 'Cardiovascular disease: risk assessment and reduction, including lipid modification' (CG181).⁶

With a growing body of evidence and increasing recognition of Lp(a) as an independent, inherited and causal risk factor for ASCVD (reflected in its inclusion within several international CVD guidelines) the expansion of CG181 to include Lp(a) would be an important step towards ensuring that patients with elevated Lp(a) levels are identified and receive enhanced cardiovascular risk factor management.⁷

This could then inform the introduction of preventative measures to help reduce the significant burden of CVD across the NHS and society.

The above calls to action are endorsed by the following members of the Lp(a) Taskforce:



About the Lp(a) Taskforce

The Lipoprotein(a) Taskforce is a diverse multi-stakeholder group encompassing patient organisations, professional societies, parliamentarians, clinical and academic medical experts and industry representatives across the lipid, cardiovascular disease, and laboratory community.

It has been constituted to recognise Lipoprotein(a) – also known as 'Lp(a)' – as a risk factor for atherosclerotic cardiovascular disease (ASCVD) and to raise awareness of the value of screening for Lp(a) in routine clinical practice to improve ASCVD management.

The Lp(a) Taskforce is a non-promotional forum and will not advocate for the use of any individual product, medicine, device, or service. Industry members of the Lp(a) Taskforce provide equal funding for the group's activity and work programme.



"As President of the British Cardiovascular Society, I am pleased to support the Lp(a) Taskforce initiative and its important and timely work to improve recognition of Lp(a) across the NHS. Lp(a) has the potential to become a leading area of CVD innovation in the UK and it is vital that healthcare professionals are equipped with the right tools to help realise this potential."

Professor John Greenwood, President of the British Cardiovascular Society

What is Lp(a) and why does it matter?

What is Lp(a)?

Lp(a) is a large lipoprotein particle which is made by the liver and found in the blood plasma.⁸ It consists of fat and proteins which carry cholesterol and other lipids through the bloodstream.⁸

Lp(a) is an independent, inherited, and causal risk factor for atherosclerotic cardiovascular disease (ASCVD).^{9,10} It subsequently serves as a vital indicator of individual susceptibility to several related events and conditions including myocardial infarction, stroke, coronary artery disease, peripheral arterial disease, and heart failure.^{7,9}

Approximately **1 in 5 people** are estimated to have elevated levels of Lp(a)⁹

Around **70-90%** of an individual's Lp(a) level is genetically determined¹⁰





It is estimated that elevated Lp(a) concentration is associated with **5% of CVD events**¹³

How does elevated Lp(a) increase CVD risk?

Lp(a) increases cardiovascular risk through three main mechanisms:



1. Pro-atherogenic: The atherogenic effects of Lp(a) lead to the <u>build-up of fatty deposits</u>

inside blood vessels.¹¹

2. Pro-inflammatory: The composition of the Lp(a) particle can lead to inflammation in the blood vessels.¹¹





3. Pro-thrombotic:

Lp(a) can interfere with the clotting process and promote the development of blood clots in the circulatory system.¹¹

Current screening for Lp(a)

Lp(a) is not routinely measured in clinical practice due to a variety of barriers including a lack of representation in appropriate UK guidelines, a lack of standardisation in screening and measurement, and the lack of therapeutic options for an individual with elevated Lp(a).^{12,13}

There are no targeted therapies that lower Lp(a) and existing treatment options are currently limited to lipoprotein apheresis, but this is both a costly and time-intensive procedure meaning it is not widely accessible across the NHS.¹⁴ A number of targeted Lp(a) lowering therapies are in development but will not be available for use for several years pending the outcome of clinical trials.¹³

Despite this, Lp(a) screening provides important opportunities to better understand individual cardiovascular risk and can help to:

- Inform more intensive ASCVD risk factor management through lifestyle modifications and other medications⁷
- Inform cascade screening of family and close relatives to understand their ASCVD risk profile¹³
- Support healthcare planning and decision-making through the wider collection of real-world evidence on the burden of Lp(a)¹³

"Although effective targeted Lp(a) lowering therapies are not yet available for use across the NHS, screening remains an important tool to support the identification of those with elevated Lp(a) who may benefit from early preventative measures such as statin therapy to reduce non-HDL cholesterol."

Dr Dermot Neely (Consultant in Clinical Biochemistry and Metabolic Medicine and Clinical Advisor to the Lp(a) Taskforce)

Call to action

Standardisation of Lp(a) screening and measurement

In the short-term, there is a need to introduce greater standardisation in the screening and measurement of Lp(a). This is particularly important in light of the growing evidence and recognition for Lp(a) as an independent, inherited, and causal risk factor for ASCVD, as demand for Lp(a) screening is anticipated to increase significantly in the coming years. As such, it is important to ensure that stakeholders work together to address current variation in the screening and measurement of Lp(a), to avoid future challenges as testing becomes more widely adopted in clinical practice.

Current Variations in Lp(a) Screening and Measurement¹⁵

Different units of measurement: There are three different units of measurement that are widely used in the context of Lp(a), including nanomoles per litre (nmol/L), milligrams per decilitre (mg/dL) and milligrams per litre (mg/L), despite recent recommendations from HEART UK and the American Heart Association to use nmol/L.^{10, 12} *

Inconsistent reporting: A recent global study of Lp(a) screening found significant variation in the reporting of Lp(a) concentration.¹⁵ 62% of patients had their Lp(a) levels measured in mass units, with this increasing to 71% in the UK.¹⁵

Test quality: Factors underpinning the quality of Lp(a) tests include the use of appropriate calibrators, the standardisation of calibration protocols, and traceability. Without these in place, Lp(a) can be both overestimated and underestimated, thereby reducing the value of Lp(a) screening in supporting clinical decision-making.¹⁶

*Lp(a) measurements according to mass units reflect the mass of the entire Lp(a) particle. This mass value assumes that the lipid components are the same in all Lp(a) particles. By contrast Lp(a) measurements according to molar units, reflect the number of circulating Lp(a) particles, thereby overcoming the potential variation in the mass of the lipid components in the Lp(a) particle. The conversion between these two values is therefore not a straightforward process and introduces the potential for inaccuracies.¹⁷



Encouraging Consistency

To address current variation in Lp(a) screening and measurement, HEART UK have recommended that:

- Screening results are expressed in nmol/L of Lp(a) particles¹¹
- Cardiovascular risk is determined according to the following thresholds of Lp(a) serum concentration: 32-90 nmol/L (minor), 90-200 nmol/L (moderate), 200-400 nmol/L (high) more than 400 nmol/L (very high)¹¹
- Screening is carried out among people with a personal or family history of premature atherosclerotic cardiovascular disease; first degree relatives with raised serum Lp(a) levels above 200 nmol/L; familial hypercholesterolemia, or other genetic dyslipidaemias; calcific aortic valve stenosis; a borderline increased (but < 15%) 10-year risk of a cardiovascular event¹¹ The Association for

The Association of Clinical Biochemistry and the Royal College of Pathologists will shortly be making a recommendation on the measurement and reporting on Lp(a), to be implemented by UK External Quality Assessment Services (NEQAS) and Wales External



Quality Assessment Services (WEQAS)*. A comment will be added to the recommendation directing any enquiries to HEART UK's guidance. This should provide the basis for more standardised reporting on Lp(a) and the wider sharing of best practice.

As part of wider efforts to improve the accuracy and consistency of Lp(a) screening across the system, codes for Lp(a) have recently been added to SNOMED CT, the most comprehensive clinical vocabulary used in electronic patient records. The addition of the two new codes, for a 'Family history of lipoprotein (a) hyperlipoproteinaemia (situation)' and for 'Lipoprotein (a) hyperlipoproteinaemia (disorder)', should help to enable the more systematic recording of whether patients or their relatives have elevated Lp(a).¹⁸

Lessons can be learnt from the efforts to improve the standardisation of NT-proBNP testing for heart failure. NT-proBNP testing has a firm place within NICE guidance for the management of patients with chronic heart failure with widely accepted thresholds for determining the need for further diagnostic tests and specialist care.¹⁵ Nanograms per litre (ng/L) is commonly used and patients are categorised according to the following thresholds:

- NT-pro-BNP level lower than 400 ng/L: Heart failure is less likely¹⁹
- NT-pro-BNP level between 400-2000 ng/L: Refer for specialist assessment and echocardiography within 6 weeks¹⁹
- NT-pro-BNP level about 2000 ng/L: Refer urgently for specialist assessment and echocardiography within 2 weeks¹⁹

"The number of laboratories measuring Lp(a) themselves is relatively small so it would be advantageous to resolve this issue now before the number of testing laboratories increases. Clinicians get used to the 'numbers' that they first used for an analyte and it is important that they don't become entrenched in using the wrong or superseded units."

Finlay MacKenzie, UK NEQAS Chemistry

Call to action

Including Lp(a) within **CVD risk calculators**

Including Lp(a) within the Joint British Societies recommendations on the prevention of Cardiovascular Disease (JBS) and QRISK has the potential to improve the accuracy of CVD risk assessments, particularly for patients who are at intermediate risk and have exhibited several clinical predictors of adverse cardiovascular events.^{2,3,4} The Lp(a) Taskforce is therefore calling for the inclusion of Lp(a) within future updates to the criteria of both risk calculators to inform improved risk factor management.⁵

The value of including Lp(a) in risk calculators

CVD risk calculators play a key role in supporting CVD prevention strategies and are used widely by clinicians across the NHS. With an accurate estimate of individual risk, patients and clinicians can be empowered to make shared decisions about lifestyle changes and appropriate treatment interventions. There is a growing body of evidence which indicates that the inclusion of Lp(a) within risk calculators can lead to an improvement in the accuracy of this vital calculation.^{20, 21, 22}

Whilst this improvement is generally modest, including Lp(a) within risk calculations has been shown to be particularly beneficial for patients who fall into the intermediate-risk category. Patients who are at intermediate risk will often be exhibiting several clinical predictors of adverse cardiovascular events, meaning their reclassification is the most clinically relevant.^{19,20} These patients can benefit from a 39% net overall improvement to the accuracy of their risk classification when Lp(a) is accounted for.²³

Improved accuracy of risk calculators subsequently has several benefits, both from a clinical and patient perspective. In particular, it can ensure that patients are classified correctly, informs the most appropriate interventions to manage risk, and leads to the more efficient use of medicines and other healthcare resources.^{21,22,23,24}

"If Lp(a) concentration was included as part of CVD risk assessment, many people at unrecognised high CVD risk would be identified for early preventative measures."

Dr Dermot Neely (Consultant in Clinical Biochemistry and Metabolic Medicine and Clinical Advisor to the Lp(a) Taskforce)





Laboratory and Point of Care products, reference laboratory, guality control production, and education and training

^{*} UK NEQAS is a charitable consortium of external quality assessment providers which assess the quality of medical tests and their reporting to ensure they are comparable, safe, and clinically useful to the patient * WEQAS, the Welsh equivalent of NEQAS, provides four distinct services including External Quality Assessment for

Avenues to include Lp(a) within CVD risk calculators

There are several potential avenues to incorporate Lp(a) within CVD risk calculators, including JBS and QRISK.^{3,4} This would reflect guidance from the European Society of Cardiology (ESC) which emphasised the importance of identifying patients with very high inherited Lp(a) levels who have an equivalent lifetime risk of ASCVD to a patient with heterozygous familial hypercholesterolaemia (HeFH), an inherited genetic disorder that causes dangerously high cholesterol levels.²⁴

JBS:

The Joint British Societies (JBS) guidance and accompanying risk calculator for the prevention of cardiovascular disease is currently being updated. As part of the update, the calculator is being expanded to present a life-time horizon of cardiovascular risk, rather than the current 10-year timeframe.³ The JBS calculator is used widely by GPs and helps practitioners to answer three kev auestions:

- Why should I start CVD risk reduction?
- When should I start?
- What should I do?

Answering these three key questions effectively leads to improved clinical decisionmaking and empowers patients and clinicians to make shared decisions about potential lifestyle changes and appropriate treatment interventions.

QRISK:

In addition to JBS, the NICE-recommended QRISK tool estimates the risk of a person developing a heart attack or stroke over the next 10 years. The most recent update to QRISK (QRISK3) included 8 additional criteria that should be factored into the estimate of overall cardiovascular risk such as migraines, measures of systolic blood pressure variability, erectile dysfunction, and chronic kidney disease.⁴ This demonstrates the precedent for updating QRISK to include new criteria and improve the accuracy of the overall calculation. Including Lp(a) has been shown to improve the accuracy of QRISK scores, and although this is modest, it can be particularly beneficial for intermediate-risk patients.^{20,22,23}

Call to action

Including Lp(a) within clinical guidelines

The Taskforce is also calling for the inclusion of specific recommendations for Lp(a) within the next update to the National Institute for Health and Care Excellence (NICE) clinical guideline on 'Cardiovascular disease: risk assessment and reduction, including lipid modification' (CG181).6

With a growing body of evidence and increasing recognition of Lp(a) as an independent, inherited and causal risk factor for ASCVD (reflected in its inclusion within several international CVD guidelines) the expansion of CG181 to include Lp(a) would be an important step towards ensuring that patients with elevated Lp(a) levels are identified and receive enhanced cardiovascular risk factor management.⁷

This could then inform the introduction of preventative measures to help reduce the significant burden of CVD across the NHS and society.

Current status

As of April 2023, there are no recommendations on Lp(a) in relevant UK guidelines such as 'Cardiovascular disease: risk assessment and reduction, including lipid modification' (CG181) and 'Familial hypercholesterolaemia: identification and management' (CG71).^{6,25} CG181 is currently being updated, and the Taskforce believes that there is an increasingly large body of evidence to justify the inclusion of Lp(a) within the guideline.²⁶





The Case for Change

The Lp(a) Taskforce is calling for a targeted update to CG181 to include relevant recommendations for Lp(a).



The status of Lp(a) as an independent, inherited, and causal risk factor for ASVCD has been increasingly recognised in recent years. For example, the number of academic publications on Lp(a) has increased by 73% since 2018 (informed by a search of Lp(a) publications on the National Library of Medicine from January 2018- December 2022).²⁷ This includes a number of publications and guidance documents calling for increased screening of CVD risk factors, including:



HEART UK's consensus statement on Lipoprotien(a): "A call to action" (2019)¹²



National Lipid Association's Scientific Statement: "Use of Lipoprotein(a) in Clinical Practice: A Biomarker whose time has come" (2019)²⁸



American Heart Association's Scientific Statement: 'Lipoprotein(a): A genetically Determined, Causal, and Prevalent Risk for Atherosclerotic Cardiovascular Disease' (2021)¹⁰



European Atherosclerosis Society's consensus statement: 'Lipoprotein(a) in atherosclerotic cardiovascular disease and aortic stenosis (2022)'7

These publications have contributed to greater awareness of the role of Lp(a), its association with ASCVD, and how to manage patients with elevated levels. Based on these publications, a growing clinical consensus has been reached around the following core recommendations:10,12,28

- Lp(a) results should be expressed in nmol/L
- Despite the absence of specific Lp(a) lowering therapies, there is value in identifying patients with high Lp(a) concentrations to inform more intensive **ASCVD** risk factor management
- Following the identification of a patient with elevated Lp(a), they should receive personalised management of their CV risk factors including blood pressure, glucose, and lifestyle.

Cost-effectiveness: Data on the cost-effectiveness of wider screening for Lp(a) is not widely available and this is an area that the Taskforce will be looking to address in the coming years. However, the cost of the test is relatively inexpensive, typically less than £25, particularly as people only need to be tested once in their lifetime.¹³ The annual burden of CVD on the UK is significant (estimates of £18 billion per year and 10.1% of total health expenditure) and even a modest improvement in ASCVD risk management from wider awareness of Lp(a) would likely lead to cost savings.¹³

The importance of system alignment

The inclusion of Lp(a) within the ongoing update to CG181 would align with recent healthcare system developments such as:



2

3

The commitment from NICE to establish living guidelines: NICE's five-year strategy from 2021 sets out the ambition of developing "more dynamic, living guideline recommendations".²⁹ This ambition is underpinned by commitments to take account of the most up-to-date evidence and data, apply agile approaches, and support shared decision-making between patients and healthcare professionals.

The focus on CVD prevention: Across the NHS, there is a clear recognition of the need to focus on CVD prevention. This was most clearly defined in the NHS Long Term Plan, which established 'CVD as the single biggest area where the NHS can save lives over the next 10 years', with the recognition that earlier detection will be vital to achieving this ambition.³⁰ The Government's Life Sciences Vision similarly identified the prevention and treatment of CVD and its major risk factors as one of seven great healthcare challenges that could benefit from new technologies and innovation.³¹

Personalised care and precision medicine: Recent years have also seen an increasing shift towards more personalised care and precision medicine in line with the roll-out of Integrated Care Systems (ICSs). CVD leads are being appointed across all of England's 42 ICSs, with the intention that this will translate into the development of regional CVD-specific plans which take account of the needs of the local population.¹This shift towards more personalised care is also reflected in the wider availability of genetic testing, with initiatives such as the Newborn screening programme working to enable the early identification and treatment of 9 rare conditions.³² Screening for genetic CVD disorders, such as FH, is also being more widely carried out across the system in line with existing NICE guidance.²⁵

Next steps for the Lp(a) Taskforce

Based on the Lp(a) Taskforce's key calls to action, the below sets out indicative timelines of when the Taskforce would like to see the implementation of each recommendation.

2023:

Lp(a) Taskforce Call to Action published

2023:

Increased standardisation of Lp(a) testing with wider uptake of HEART UK guidance



Lp(a) included within risk calculators

2024/25: Lp(a) incorporated within relevant NICE guidance (CG181)

2025:

• Inclusion of Lp(a) testing and management approaches within ICS CVD planning/pathway development

Routine screening of Lp(a) across NHS



Annex

The Lp(a) Taskforce is comprised of the following member organisations:

- Ms Jules Payne, Chief Executive, HEART UK (CHAIR)
- Dr Mayur Patel, Director of Clinical Practice, Association of Clinical Biochemistry and Laboratory Medicine
- Professor John Greenwood, President, British Cardiovascular Society
- Professor Charalambos Antoniades, Chair, British Atherosclerosis Society
- Dr Lance Sandle, Registrar, Royal College of Pathologists
- Dr Jaimini Cegla, Vascular, Lipid and Metabolic Medicine Section, Royal Society of Medicine
- Mr Finlay MacKenzie, Director and Consultant Clinical Scientist, UK NEQAS Chemistry, Birmingham
- Ms Annette Thomas, Director, WEQAS
- Mr Steve Richardson, Public Affairs Lead, Novartis Pharmaceuticals
- Ms Jacqui Young, Public Affairs Manager, Roche
- Ms Claire Huguet, Head of Biomarker Services, Randox
- Mr Mazhar Iqbal, Medical Development Director, Amgen

Contact information

Secretariat services for the Lp(a) Taskforce are provided by HEART UK with support from M+F Health Communications Ltd. For any further information about the Taskforce, please contact <u>lpa@mandfhealth.com</u>.

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Lp(a) Taskforce Call to Action : Glossary of terms

Apheresis: A form of medical technology where a patient's blood is passed through an apparatus that separates out one particular constituent from the blood and returns the remainder for normal circulation.

Atherosclerosis: The build up of fatty material called atheroma or plaque in the artery walls leading to the narrowing of arteries until blood can't pass properly from the heart to the rest of the body.

Calcific aortic valve stenosis: A type of heart valve disease where the valve between the lower left heart chamber and the aorta is narrowed and doesn't open fully, reducing the blood flow from the heart to the aorta and the rest of the body.

Calibrators: Lp(a) calibrators are used to ensure that the reading is accurate at the point of delivery to a patient in line with the test manufacturer's tolerances.

Coronary artery disease: A common but serious condition where the blood vessels supplying the heart are narrowed or blocked.

Familial hypercholesterolemia: An inherited condition that is caused by a genetic mutation which means that your liver is unable to remove excess cholesterol from the blood, known as LDL.

Genetic dyslipidaemias: A single genetic mutation in one of several genes that leads to individuals having abnormal blood lipid levels and can contribute to the early onset of CVD.

Isoform sensitivity: This refers to whether Lp(a) tests are sensitive to the variation in the size of the apo(a). This sensitivity can lead to variation in reporting meaning gold standard Lp(a) tests use isoform insensitive assays.

Joint British Societies recommendations on the prevention of cardiovascular disease (JBS): A risk calculator managed by the British Cardiovascular Society and supported by the British Heart Foundation which aims to provide patients with a better understanding of their personal CVD risk to inform appropriate decisions about lifestyle changes and treatment interventions.

Low-density-lipoprotein Cholesterol (LDL-C): Often referred to as 'bad' cholesterol, LDL-C contributes to atherosclerosis, narrowing the arteries and increasing the risk of a heart attack, stroke and peripheral artery disease.

Myocardial infarction: The scientific term for a heart attack, when blood flow decreases or stops to the coronary artery of the heart, causing damage to the heart muscle.

NT-proBNP testing: One of the main diagnostic methods for heart failure which measures the levels of brain natriuretic peptide (BNP) and N-terminal pro b-type natriuretic peptide (NT-proBNP) in your blood. High levels of either can indicate that the heart isn't pumping as much blood as the body needs.

Peripheral arterial disease: A common condition where the build-up of fatty deposits in the arteries restricts blood supply to the leg muscles.

QRISK: The NICE-recommended prediction algorithm which assesses a variety of health and lifestyle factors to establish an individual's risk of developing a heart attack or stroke over the next 10 years.

Serum concentration: The cardiovascular risk conferred by Lp(a) is determined by an individual's serum concentration.

Traceability: This aims to reduce variation in Lp(a) testing methods so that results are independent of time and location.

UK External Quality Assessment Services (UK NEQAS): A charitable consortium of external quality assessment providers which assess the quality of medical tests and their reporting to ensure they are comparable, safe, and clinically useful to the patient.

Wales External Quality Assessment Services (WEQAS): The Wales equivalent of NEQAS which provides four distinct services including External Quality Assessment for Laboratory and Point of Care products, reference laboratory, quality control production, and education and training.

