

Review article

HEART UK consensus statement on Lipoprotein(a): A call to action



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HIGHLIGHTS

- The cardiovascular risk conferred by lipoprotein(a) is determined by the lipoprotein(a) serum concentration.
- Serum lipoprotein(a) levels should be measured in five specific population groups.
- Recommendations on the management of patients with raised lipoprotein(a) levels (> 90 nmol/l) are discussed.

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ABSTRACT

Lipoprotein(a), Lp(a), is a modified atherogenic low-density lipoprotein particle that contains apolipoprotein(a). Its levels are highly heritable and variable in the population. This consensus statement by HEART UK is based on the evidence that Lp(a) is an independent cardiovascular disease (CVD) risk factor, provides recommendations for its measurement in clinical practice and reviews current and emerging therapeutic strategies to reduce CVD risk. Ten statements summarise the most salient points for practitioners and patients with high Lp(a).

HEART UK recommends that Lp(a) is measured in adults as follows: 1) those with a personal or family history of premature atherosclerotic CVD; 2) those with first-degree relatives who have Lp(a) levels > 200 nmol/l; 3) patients with familial hypercholesterolemia; 4) patients with calcific aortic valve stenosis and 5) those with borderline (but < 15%) 10-year risk of a cardiovascular event. The management of patients with raised Lp(a) levels should include: 1) reducing overall atherosclerotic risk; 2) controlling dyslipidemia with a desirable non-HDL-cholesterol level of < 100 mg/dl (2.5 mmol/l) and 3) consideration of lipoprotein apheresis.

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1. Background

Although Lipoprotein(a) (Lp(a)) is now established as a causal risk factor for cardiovascular disease (CVD) [1–3], there is little consensus between the different national guidelines on how to use this information on Lp(a) to more accurately estimate and modify cardiovascular risk [4,5]. For instance, the 2012 Australian Guideline does not mention Lp(a) [6]. On the other hand, the 2019 European Guideline on CVD prevention in clinical practice suggests measuring Lp(a) at least once in each adult person's lifetime⁷. The 2016 Canadian Cardiovascular Society Guideline also adopts a similar approach [8]. The 2018 American College of Cardiology/American Heart Association Guideline on blood cholesterol defined Lp(a) as a 'risk-enhancing factor', especially at higher levels of Lp(a) [9]. In part these differences in national statements reflect, as acknowledged by the National Heart, Lung and Blood Institute's Lp(a) working group, gaps in our knowledge of how Lp(a) mechanistically contributes to CVD and calcific aortic valve disease (CAVD) [10].

The importance of reducing Lp(a) associated cardiovascular risk requires a reappraisal for four main reasons: 1) genetic studies have demonstrated an unequivocal strong link between genes associated with increased Lp(a) and cardiovascular risk [3,11,12] and as well as the protective effect of *LPA* null alleles or other strongly Lp(a)-decreasing alleles and CVD risk [13,14]; 2) new insights into Lp(a) assay methodology suggest that inaccurate quantitation of Lp(a) has led historically to its underestimation as a cardiovascular risk factor [10,15]; 3) Lp(a) contributes to aortic valve calcification [16–18] and 4) the emergence of effective therapies for reducing Lp(a) levels [19]. In this statement we advocate more widespread clinical use of Lp(a) data to refine assessment of cardiovascular risk (Table 1) based on its accurate and reliable measurement.

Lp(a) is a LDL-like particle, with a single apolipoprotein B100 (apoB), covalently linked by a disulphide bond to a single apolipoprotein(a) (apo(a)) (Fig. 1). The molecular mass of apo(a) can vary between 275 and 800 kDa [20,21] due to the inheritance of > 40 different allelic *LPA* variants encoding different numbers of kringle IV type 2 repeat sequences in this polypeptide [22]. The rate of apo(a) synthesis and secretion is inversely related to its molecular mass, and consequently, individuals who produce the lower molecular mass apo(a) isoforms have higher serum Lp(a) levels than those who produce the higher molecular mass isoforms [21,23,24]. Indeed, this explains the results of early genetic studies which established that serum Lp(a) levels are predominantly genetically inherited in an autosomal co-dominant manner [20,21,25] and that allelic variation at the *LPA* locus is largely responsible for the wide, potentially as much as 1000-fold differences in serum Lp(a) levels [12,26,27].

2. Epidemiology

It is now well-established that serum Lp(a) concentrations and their distribution vary with ethnicity and local population structures. The apo(a)-size allele affects serum Lp(a) concentrations to different degrees in different populations, with one study reporting that the variation in KIV-2 repeat number accounted for 63.2% of the total variability in Lp(a) levels in Caucasians and just 38.6% in African Blacks [28]. In Caucasians, 80% of the population have a serum Lp(a) < 90 nmol/l (40 mg/dl) and the distribution is positively skewed [12], however, people of African descent have levels twice as high as Caucasians, Hispanics and certain Asian populations, whereas South Asians have intermediate levels [1,29–32]. No sex-specific differences in distributions of Lp(a) levels have previously been noted [33]. However, recent large studies have suggested that women have slightly higher levels than men [34–36].

Historically, progress in establishing the contribution of Lp(a) in CVD pathogenesis has been compromised by lack of standardised methods for measuring serum levels of this atherogenic lipoprotein (see

Table 1

Ten statements on Lipoprotein(a) from HEART UK.

1. Lipoprotein(a) is an independent risk factor for cardiovascular disease and calcific aortic valve stenosis.
2. The cardiovascular risk conferred by lipoprotein(a) is determined by the lipoprotein(a) serum concentration: 32–90 nmol/l minor; 90–200 nmol/l moderate; 200–400 nmol/l high; > 400 nmol/l very high.
3. Lipoprotein(a) levels are genetically determined with an autosomal co-dominant inheritance.
4. Secondary causes of high lipoprotein(a) should be sought and, if possible, corrected.
5. Regarding measurement:
 - a) Serum Lipoprotein(a) concentrations should be measured using a method where the effect of isoform size has been minimized using appropriate antibodies with calibrators certified for traceability of Lp(a) values to the WHO/IFCC reference material.
 - b) Results should be expressed in nmol/l of Lp(a) particles.
 - c) Conversion of mass units to molar units or vice versa introduces inaccuracy and should be discouraged.
 - d) Currently only assays based on Denka reagents with calibrators traceable in nmol/L to WHO/IFCC reference material can be recommended.
6. Lipoprotein(a) levels need only be measured once, unless a secondary cause is suspected or specific treatment is instituted in order to lower levels.
7. Serum Lipoprotein(a) levels should be measured in those with:
 - a) a personal or family history of premature atherosclerotic cardiovascular disease (< 60 years of age)
 - b) first degree relatives with raised serum Lp(a) levels (> 200 nmol/l)
 - c) familial hypercholesterolemia (FH), or other genetic dyslipidemias
 - d) calcific aortic valve stenosis
 - e) a borderline increased (but < 15%) 10-year risk of a cardiovascular event
8. The management of patients with raised lipoprotein(a) levels (> 90 nmol/l) should include:
 - a) reducing overall atherosclerotic risk
 - b) controlling hyperlipidemia
 - c) consideration of lipoprotein apheresis as per the HEART UK Lipoprotein apheresis statement [58].
9. In patients with raised Lipoprotein(a) levels (> 90 nmol/l), desirable non-HDL-cholesterol is < 100 mg/dl (2.5 mmol/l).
10. Future work needs to focus on:
 - a) Development of commercial truly isoform insensitive assays
 - b) randomised, controlled interventional studies that selectively lower Lipoprotein(a) in primary and secondary prevention of ASCVD
 - c) the role of antiplatelet therapy in primary prevention
 - d) Lipoprotein(a) reference ranges in different ethnic groups

*The 2016 ACC/AHA Clinical Guideline Recommendation Classification System has been followed to assess strength of recommendation and guide the phrasing of the recommendation.

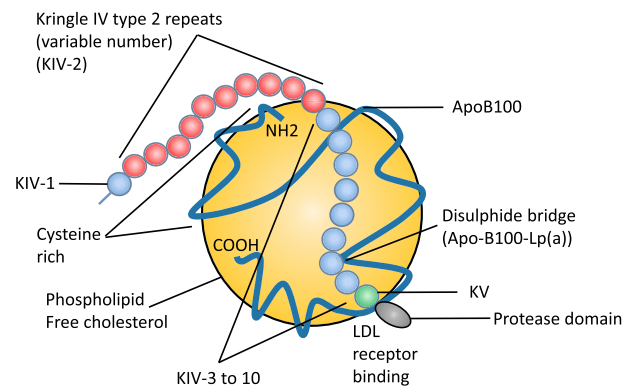


Fig. 1. The structure of Lipoprotein(a).

The Lp(a) particle contains a single molecule of apo(a) and the 4536 amino acid apoB100 polypeptide (blue ribbon), which forms a ribbon and bow-like structure around the cholesteryl-ester core of the LDL component of this particle. Apo(a) contains 10 classes (coloured balls) of kringle modules, designated KIV-1-10, KV and a protease domain. The variable number of KIV-2 modules forms the basis of the observed isoform size heterogeneity of apo(a), which may impact on the non-covalent interactions between this molecule and apoB. There is a disulphide bond formed between a free cysteine in KIV-9 and the apoB100 cysteine 4326.

Measurement of Lp(a) section below), with the consensus being that estimates based on these data underestimated the importance of Lp(a) as a cardiovascular risk factor [15]. In 2003, WHO accepted protocols for standardisation of Lp(a) assays, which now allows its more reliable quantification. Although there remain large differences between assays, these protocols have reduced the bias caused by isoform size of Lp(a) and have made within study comparisons more robust [15]. Hence, in the past decade there has been consolidation of the evidence that elevated serum Lp(a) is a risk factor for coronary heart disease (CHD), ischaemic stroke, peripheral artery disease, as well as calcific aortic valve stenosis [11,12,37,38]. Moreover, Mendelian randomisation studies and genome wide association studies support Lp(a) as an independent cardiovascular risk factor^{12 11}. Thus, the principles behind current methodologies and the inherent difficulties in fully capturing the unique lipid and structural properties of Lp(a) particles (Fig. 1) are discussed in the context of our Statement 5.

In 2009, the Emerging Risk Factors Collaboration (ERFC) published a meta-analysis of 39 long-term prospective studies, that comprised a total of 126,634 individuals (1.3 million person-years of follow-up) with recorded baseline serum Lp(a) concentration and subsequent major vascular morbidity and/or mortality data [38]. Serum Lp(a) levels were consistent within individuals over a period of several years. The risk ratio for CHD, adjusted for age and sex, was 1.16 (95% CI, 1.11–1.22) per 3.5-fold higher usual Lp(a) levels (ie, per 1 SD), and 1.13 (95% CI, 1.09–1.18) after further adjustment for traditional risk factors. The corresponding adjusted risk ratios were 1.10 (95% CI, 1.02–1.18) for ischaemic stroke, 1.00 (95% CI, 0.97–1.04) for cancer deaths, and 1.00 (95% CI, 0.95–1.06) for nonvascular deaths other than cancer. Thus, there was a continuous and independent association of serum Lp(a) concentration with risk of CHD and stroke. Moreover, it is likely that published meta-analyses of Lp(a)-conferred risk, such as the ERFC, have underestimated Lp(a)-conferred risk due to the incorporation of studies using isoform biased assays.

Lp(a) is also a potent risk factor for calcific aortic valve stenosis [16,37]. Data from the ASTRONOMER trial, which included patients with mild-moderate aortic stenosis, found that patients with the highest levels of Lp(a) (> ~150 nmol/l (> 58.5 mg/dl)) had a greater rate of disease progression and need for earlier valve replacement [17].

3. Genetics and secondary causes of elevated Lp(a)

The epidemiological findings from the ERFC [38] that elevated Lp(a) levels constitute a major independent risk factor for CHD and stroke are corroborated by the results of genetic studies which provide evidence that LPA-Lp(a) raising variants increase CHD [39]. In 2009, Kamstrup et al. published a Mendelian randomisation study involving 40,000 participants from the Copenhagen City Heart Study (CCHS), the Copenhagen Ischaemic Heart Disease Study (CIHDS) and Copenhagen General Population Study (CGPS) [12]. In all three cohorts, there was strong association between plasma Lp(a) levels and the LPA kringle IV type 2 (KIV-2) copy number variation (calculated as the sum of KIV-2 repeats of the two alleles); for example, in the CGPS contingent, this size variation explained ~27% of the variance in Lp(a) levels. Moreover, a lower KIV-2 copy number, and hence higher Lp(a) concentration, was associated with a significantly higher risk of myocardial infarction (MI) in this study. In particular, an Lp(a) level > 95th percentile had a 3- to 4-fold increase in multi-factorial-adjusted risk of MI and absolute 10-year risks of 20% and 35% in high risk women and men [40]. Conversely, individuals with a common null LPA allele, and consequently low Lp(a) levels, had reduced CVD risk (odds ratio, 0.79 (95% CI 0.66–0.97)) compared with non-carriers, providing further support for a causal role of Lp(a) in CVD [41].

Besides the KIV-2 copy number variation, two LPA single nucleotide polymorphisms (SNP) were found by a candidate gene association study to display association with higher serum Lp(a) levels and increased CHD risk [11]. In outline, SNP rs10455872 and rs3798220 accounted

for 25% and 8% of the variation in serum Lp(a) levels, respectively. Similarly, a subsequent larger-scale genome wide association study, involving 63,746 individuals with CHD and 130,681 controls, showed that the loci most strongly associated with CHD were in the LPA region and not in other loci that are well known to be associated with increased CHD risk, such as LDL-R and PCSK-9 [42].

Although Lp(a) concentrations are predominantly (70 to > 90%) under genetic control [25], some non-genetic factors are known to influence it. In chronic kidney disease, serum Lp(a) concentrations rise with falling glomerular filtration rate due to reduced catabolism of the larger isoforms [43]. Renal transplantation appears effective at returning Lp(a) concentration to baseline [29]. Serum Lp(a) levels are fourfold higher in individuals with nephrotic range proteinuria than controls and this appears to be due to increased rates of Lp(a) synthesis across all isoform sizes although reduced catabolism may also play a role [29]. Lp(a) levels are reduced in most forms of liver disease but show weak, positive association with biomarkers of inflammation [29]. Serum Lp(a) levels, which are increased in patients with overt hypothyroidism, are reduced by levothyroxine replacement, but in sub-clinical hypothyroidism do not change significantly [44]. Serum Lp(a) levels are not consistently associated with age or gender but levels are significantly reduced by hormone replacement in postmenopausal women [45]. Thus, secondary causes of high Lp(a) such as chronic kidney disease, nephrotic syndrome and hypothyroidism should be sought and corrected.

4. Pathogenicity

Lp(a) promotes atherosclerosis by two principal mechanisms [46,47]. As an LDL-like particle, Lp(a) can infiltrate into the arterial intima and bind components of the extracellular matrix, enhancing macrophage infiltration and smooth muscle proliferation [48]. Within the atherosclerotic plaque of coronary lesions and carotid endarterectomy specimens, a substantial proportion of circulating oxidised phospholipids reside on Lp(a). These oxidised phospholipids are implicated in driving monocyte trafficking into the arterial wall and enhancing pro-inflammatory cytokine release [47]. Secondly, through its similarity to plasminogen, Lp(a) is envisaged to have a pro-thrombotic effect by inhibiting fibrinolysis. Apo(a) may also promote platelet aggregation by mediating the binding of Lp(a) to plasminogen receptors on the platelet surface and granule release via the thrombin receptor. Some biochemical studies have also demonstrated anti-fibrinolytic effects of Lp(a) [46].

4.1. Lp(a)-associated risk

The risk conferred by serum Lp(a) depends on its serum concentrations, those with most severely elevated Lp(a) being at greatest risk of CVD [12]. We propose that the graded impact of elevated serum Lp(a) concentrations on this risk be classified as follows: 32–90 nmol/l minor; 90–200 nmol/l moderate; 200–400 nmol/l high; > 400 nmol/l very high (Table 2). These cut-offs expressed in molar units are derived from population percentiles of Lp(a) measured in nmol/l and mg/dl from 13,900 participants (Nov. 2015 to June 2017) in the on-going Copenhagen General Population Study, described above [12]. Measurements were performed with the Roche assay on a Cobas platform calibrated in nmol/l (unpublished data, courtesy of P. Kamstrup and B. Nordestgaard). It must be noted that this dataset derives predominantly from Danish Caucasian populations and further work on establishing clinically relevant Lp(a) cut-off values in a range of ethnicities is still warranted (discussed in ‘Further Work’). Recognising the importance of elevated Lp(a), in October 2018 the Center for Disease Control and Prevention instituted two ICD-10 codes for diagnosis of elevated Lp(a).

Statement 1. Lipoprotein(a) is an independent risk factor for CVD and calcific aortic valve stenosis.

Table 2

The cardiovascular risk conferred by lipoprotein(a) is graded dependent on the lipoprotein(a) level.

Lp(a) level nmol/l ^a	Lp(a) level approx. in mg/dl ^b	Percentile of general population [12]	Impact on CV risk
32–90	18–40	67–80th	Minor
90–200	40–90	80–95th	Moderate
200–400	90–180	95–99.8th	High
> 400	> 180	> 99.8th	Very High

^a Percentile cutpoints in nmol/l and mg/dl for Lp(a) values derived from 13,900 participants (Nov. 2015 to June 2017) in the on-going Copenhagen General Population Study. Measurements were performed with the Roche assay on a Cobas platform (unpublished data, courtesy of P. Kamstrup and B. Nordestgaard).

^b The factor to convert Lp(a) values from nanomoles per liter of apo(a) to milligrams per deciliter is for guidance only and should not be applied to data generated with other methods because it is assay specific [86] and dependent on: 1) the size of apo(a) in the samples and 2) how the target values in mg/dl were assigned to the assay calibrators.

Statement 2. The CV risk conferred by Lp(a) is determined by the Lp(a) serum concentration: 32–90 nmol/l minor; 90–200 nmol/l moderate; 200–400 nmol/l high; > 400 nmol/l very high.

Statement 3. Lipoprotein(a) levels are genetically determined with an autosomal co-dominant inheritance.

Statement 4. Secondary causes of high lipoprotein(a) should be sought and, if possible, corrected.

5. Measurement of Lp(a) and challenges

Lp(a) expressed in mass units (mg/dl) encompasses the mass of the entire particle; this comprises apo(a), apoB-100, cholesterol, cholesteryl esters, phospholipids and triglycerides. Because of the heterogeneity in apo(a) size and the presence in most individuals of two different, genetically determined apo(a) isoform sizes, standardisation using a single calibrant material is impossible.

Furthermore, variable numbers of repeated KIV-2 units in Lp(a) act as multiple epitopes in immunoassays. Unless calibrants have the same range of isoforms as test samples, serum levels of Lp(a) in those with higher numbers of KIV-2 repeats will be overestimated and those with smaller numbers underestimated. As smaller isoforms are strongly associated with higher serum concentrations, there will be greater underestimation of Lp(a) at higher concentration than at lower ones. This leads to an under-estimation of Lp(a) associated CVD risk: it is very unlikely to be overestimated [15,49]. Furthermore, there is some evidence that smaller isoforms are more atherogenic [2] and so this effect could be exacerbated.

No available commercial immunoassays employ isoform insensitive antibodies. The gold standard method at the moment is the Northwest Lipid Metabolism and Diabetes Research Laboratory (NLM DRL) method that uses an isoform insensitive antibody and is meticulously calibrated with well characterized material, however this assay is not commercially available. Transferring values using this method to WHO/IFCC-verified reference material and calibrators have made assay measurements more uniform. Assays using Denka reagents are the most reliable commercial assays available. There are several explanations for this. The effect of isoform size has been reduced by use of a range of calibrators prepared from separate pools of serum covering a range of Lp(a) concentrations. As concentration and isoform size are inversely correlated this better matches calibrants with test samples. Even so, molar mass ratios have been shown to increase with increasing molar concentration of Lp(a) measured by the NLM DRL assay. Again as isoform size and molar concentration are inversely correlated the mass per

particle at higher concentrations will be less. Over estimation of larger isoforms will have the same effect and be more prominent at lower concentration. A further source of variability in molar mass ratio is the assignment of values in mass units to commercial calibrators. Because test samples contain a mixture of isoforms of Lp(a) it is impossible to convert mass units to molar units without detailed knowledge of the isoform composition. This problem is obviated by manufacturing materials calibrated in molar units traceable to WHO/IFCC verified reference materials in molar units. Methods based on Denka reagents calibrated in nmol/L and traceable to WHO/IFCC reference material have acceptable bias compared with the NLM DRL gold standard method [15].

Statement 5. Regarding the measurement of Lp(a):

- Serum Lipoprotein(a) concentrations should be measured using a method where the effect of isoform size has been minimized using appropriate antibodies with calibrators certified for traceability of Lp(a) values to the WHO/IFCC reference material.
- Results should be expressed in nmol/l of Lp(a) particles.
- Conversion of mass units to molar units or vice versa introduces inaccuracy and should be discouraged.
- Currently only assays based on Denka reagents with calibrators traceable in nmol/L to WHO/IFCC reference material can be recommended.

6. In whom should Lipoprotein(a) levels be measured?

Serum Lp(a) levels remain relatively stable over a lifespan [29] because they are predominantly genetically determined. Measuring serum Lp(a) concentrations as a proxy for its genetic determinants is practical and more cost effective than genetic testing at the current time. To improve the accuracy of cardiovascular risk assessment a single measurement of serum Lp(a) is sufficient for most patients. Although we have indicated broad ranges of Lp(a) concentrations associated with increasing cardiovascular risk, clinical judgement needs to be exercised for values at the cut-points. The overall precision of repeat measurement in an individual should be sufficient to base decisions on a single measurement, however, qualification of levels that are close to action thresholds should to be considered on a case-by-case basis. Repeat measurement is only indicated if a secondary cause is suspected or therapeutic measures to lower levels have been instigated.

Our recommendation for once-only measurement of Lp(a) is consistent with the recently published European guideline [7], however, we recommend that Lp(a) is only measured in specific cohorts (see following paragraphs) rather than in all adults. Population screening of Lp(a) is not currently advocated by the HEART UK consensus panel. The European guideline aims to identify those with very high Lp(a) (> 430 nmol/L). In contrast, we argue that the risk conferred by Lp(a) occurs at a much lower Lp(a) threshold than this. Therefore, our approach is to measure Lp(a) in targeted populations and manage Lp(a)-associated risk in those with levels > 90 nmol/l.

In patients with a family history of premature CVD (< 60 years), particularly when a causative mutation for Familial Hypercholesterolemia (FH) has not been identified, a knowledge of their Lp(a) value may help both the patient and physician to understand the basis of the familial CV risk. This improved understanding may also influence an individual's decision to start and adhere to long-term medication.

A role for formal family cascade testing for raised serum Lp(a) has not yet been established. However, given the dominant inheritance of Lp(a) levels, the testing of family members of index cases with severely raised levels (> 200 nmol/l) may be useful. Genetic testing for SNPs associated with serum Lp(a) levels is not currently advocated in routine clinical practice.

Patients with heterozygous FH (HeFH) have higher levels of serum

Lp(a) compared to their non-affected siblings [50]. Lp(a) is a strong risk factor for CHD in patients with HeFH, independent of age, sex, smoking status, and serum LDL-C levels [51,52]. Thus, knowledge of a FH patient's Lp(a) levels would inform the physician further regarding the patient's risk of a CVD event and on the potential benefits of a more aggressive approach to manage their hyperlipidaemia and any other unaddressed CVD risk factors [53]. Serum Lp(a) is not a predictor of CHD in homozygous FH patients on currently available cholesterol-lowering treatment, but may become so when lower levels of LDL-C are achieved [54]. On this basis, it is recommended that Lp(a) levels should be measured in those with familial hypercholesterolemia and other genetic dyslipidemias (including familial combined hyperlipidaemia, familial dysbetalipoproteinaemia, and familial hypertriglyceridaemia) which also increase CV risk.

Lp(a) is a potent risk factor for calcific aortic valve stenosis [16,37]. The knowledge of a patient's Lp(a) levels could inform selection of the interval for valve surveillance of those with established aortic valve disease as patients with raised Lp(a) are likely to require earlier intervention.

Lp(a) best re-classifies CVD risk in people at intermediate risk [55]. Patients with > 15% risk of a CV event over 10 years should be receiving treatment such as statin therapy irrespective of Lp(a) level. In the UK, uptake of statin therapy for primary prevention of CVD in patients of intermediate risk is poor, with only 14% of patients with a 10 year CV risk of between 10 and 19.9% initiated on a statin in one study [56]. The addition of serum Lp(a) measurement, at least up to the midpoint of this range, would aid reclassification of people at intermediate risk and could encourage initiation and acceptance of LDL-C-lowering therapies.

Statement 6. Lipoprotein(a) levels need only be measured once, unless a secondary cause is suspected or specific treatment is instituted in order to lower levels.

Statement 7. Serum Lipoprotein(a) levels should be measured in those with:

- a. A personal or family history of premature atherosclerotic cardiovascular disease (< 60 years of age)
- b. First degree relatives with raised serum Lp(a) levels (> 200 nmol/l)
- c. Familial hypercholesterolemia (FH), or other genetic dyslipidemias
- d. Calcific aortic valve stenosis
- e. A borderline increased (but < 15%) 10-year risk of a cardiovascular event

7. Management of patients with raised Lipoprotein(a)

A major challenge in establishing the role of Lp(a) as an important cardiovascular risk factor has been the lack of effective treatments to reduce Lp(a) levels. As a consequence, there is a paucity of evidence that decreasing serum Lp(a) levels reduces cardiovascular risk and clinical outcome trials of specific Lp(a)-lowering therapies are eagerly awaited. In the last 5 years, several novel lipid-lowering agents that can lower Lp(a) have emerged but of these, only two monoclonal antibody PCSK-9 inhibitors have been licensed for general use. Furthermore, Mendelian randomisation studies suggest a large absolute reduction in Lp(a) may be required to produce clinically meaningful reduction in CV risk [3,57]. The various therapeutic strategies for management of patients with raised Lp(a) are outlined here and summarised in Table 3. Our current recommendation for managing patients, in both primary and secondary prevention, with raised Lp(a) levels (> 90 nmol/l) includes: 1) reducing overall atherosclerotic risk 2) controlling dyslipidemia and 3) consideration of lipoprotein apheresis as per the HEART UK Lipoprotein apheresis statement [58].

Reducing CVD risk and controlling dyslipidaemia. This pragmatic approach does not directly target Lp(a) levels but addresses dyslipidemia

and other modifiable CVD risk factors, such as blood pressure and smoking with the aim of mitigating the risk conferred by Lp(a). In the EPIC-Norfolk study, patients with raised Lp(a) with the healthiest cardiovascular health score (including body mass index, healthy diet, physical activity, smoking status, blood pressure, diabetes and cholesterol levels) had substantially reduced CVD risk compared to participants in the unhealthiest cardiovascular health score category. This highlights the importance of maintaining a healthy lifestyle for patients with raised Lp(a) [59]. Aggressive LDL-C lowering can mitigate the CVD risk conferred by Lp(a) [60,61]. However, studies such as AIM-HIGH suggest that even at low LDL-C (or low non-HDL-C levels), patients with high Lp(a) fare worse than their counterparts with low Lp(a) levels [62] implying incomplete elimination of the risk conferred by elevated Lp(a) levels. Similarly, Wei et al. [63] have recently demonstrated persistence of the association between LPA genetic variants and CVD events in individuals with LDL-C \leq 70 mg/dl who were taking statins. A meta-analysis of statin-treated patients with elevated lipoprotein(a) also showed an association with cardiovascular disease risk [64]. Recent work suggests that statins may actually modestly increase Lp(a) levels, possibly by increasing Apo(a) expression, however, this requires further study [65].

Apheresis. The HEART UK Lipoprotein apheresis guidelines recommend that apheresis should be considered for those patients with progressive coronary disease and Lp(a) greater than \sim 150 nmol/l (> 60 mg/dl) whose LDL-C remains 125 mg/dl (3.3 mmol/l) despite maximal lipid-lowering therapy [58]. In Germany, Lp(a) levels exceeding \sim 150 nmol/l (60 mg/dl) along with progressive CVD (regardless of LDL-C levels) has been approved as an indication for regular lipoprotein apheresis since 2008. Studies on such patients undergoing regular apheresis suggest a reduction in cardiovascular risk [66–68]. Unfortunately, studies to date using lipoprotein apheresis have not included a simultaneous control group, therefore, it is difficult to estimate the magnitude of benefit. Lipoprotein apheresis was recently employed in patients with refractory angina and raised Lp(a) in a randomised, controlled, cross-over trial and found to improve myocardial perfusion, atheroma burden and exercise capacity [69]. Thus, although apheresis may be of cardiovascular benefit in those with raised Lp(a), access to this form of treatment is currently limited by cost and few centres are able to offer it.

The following interventions for the management of Lp(a) are NOT currently recommended by the group, however, the evidence for their use (or lack of) is summarised below:

Niacin. Until recently, niacin was used to treat high Lp(a) levels, reducing levels by 30–40% [70]. However, the use of niacin is not supported by HEART UK based on AIM-HIGH [71] and HPS2-THRIVE [72] trial findings. Niacin increased the risk of serious adverse events and did not reduce the risk of a major vascular event, leading to its withdrawal by the European Medicines Agency (EMA) in 2013.

Aspirin. Aspirin is used in clinical practice to counter the pro-thrombotic risk conferred by Lp(a). However, the efficacy of this has not been tested prospectively. In the Women's Health Study, carriers of an LPA variant associated with elevated Lp(a) levels had a doubling of cardiovascular risk and appeared, on retrospective analysis, to benefit more from aspirin than non-carriers [73]. Two recent randomised controlled trials on the use of aspirin in primary prevention, one involving patients with moderate cardiovascular risk [74] and the other in an elderly population [75], failed to show a favorable benefit:risk ratio although a sub-group analysis stratified by Lp(a) levels remains to be performed. Further prospective studies investigating the effect of aspirin in patients with elevated Lp(a) are warranted. Aspirin may also reduce Lp(a) levels by reducing apo(a) expression [76] although the evidence for this has come from very small studies [77] and requires confirmation.

Licensed novel agents. Monoclonal antibodies to proprotein convertase subtilisin/kexin type 9 (PCSK9), such as evolocumab and alirocumab, can reduce Lp(a) concentrations by 20–30% [78]. In

Table 3
Summary of therapeutic strategies to reduce Lipoprotein(a) (Lp(a)) levels.

Drug/Intervention	Lp(a) reduction	In current clinical use for treatment of Lp(a)	CV data	Reference(s)
Niacin	20–30% [70]	No – withdrawn by EMA	No effect on CVD when added to statin therapy [71,72]	Carlson et al., J Int Med 1989 [70] Boden et al., NEJM 2011 [71] Laudray et al., NEJM 2014 [72]
Aspirin	20% reduction at 6 months [77]	Yes	> 2 fold reduction in CV events in carriers of rs3798220 ⁷³	Akaike et al., Clin Chem 2002 [77] Chasman et al., Atherosclerosis 2009 [73]
Lipoprotein apheresis	~50% reduction post-apheresis depending on method [58]	Yes	Annual MACE rate reduction by 85% [67]	Thompson et al., Atherosclerosis 2008 [58]
Lp(a) apheresis	75% reduction post-apheresis [87]	No	Reduction in atherosclerotic burden in coronary and carotid arteries [87]	Roeseler et al., ATVB 2016 [67] Pokrovsky et al., Atherosclerosis supp 2017 [87]
PCSK-9 inhibition	20–30% [78]	No	Reduction in CV mortality [88]	Raal et al., JACC 2014 [78] Sabatine et al., NEJM 2017 ⁸⁸
Mipomersen	20–30% [89]	No –not licensed by EMA	Reduction in MACE in FH patients [90]	Santos et al., ATVB 2015 [89] Duell et al., J Clin Lipidology 2016 [90]
Anacetrapib	~35% [91]	No – stopped in development	Reduction in major coronary events [92]	Cannon et al., NEJM 2010 [91] Laudray et al., NEJM 2017 [92]
Antisense to Lp(a)	Up to 99% [19]	No	No	Viney et al., Lancet 2016 [19]
Bariatric surgery	30% (RYGB) and 5% (SG) reduction at 6 months post surgery [93]	No	No	Weiss et al., Am Heart J, 2018 [93]
Eprotirome	43% [94]	No– stopped in development	No	Ladenson et al., NEJM 2010 [94]
HRT (Estrogen and progesterone)	15–20% [95]	No	No	Shlipak et al., JAMA 2000 [95]

CVD Cardiovascular disease; MACE Major adverse cardiovascular event; EMA European Medicines Agency; FH Familial hypercholesterolemia; RYGB Roux-en-Y gastric bypass; SG Sleeve gastrectomy; HRT Hormone replacement therapy.

exploratory analyses in clinical trials, CV event risk reduction appeared greater in treated subjects with higher Lp(a), but these agents are not currently licensed for lowering Lp(a) [79,80]. It is uncertain as to how much of the absolute risk reduction attributable to PCSK9 inhibition, which is higher in patients with high Lp(a), is explained by Lp(a) reduction or simply due to LDL-C lowering, given that patients with high Lp(a) levels are at higher absolute risk of CVD.

Novel agents in development. Antisense oligonucleotides targeting hepatic *LPA* RNA reduce apo(a) production and Lp(a) assembly with apoB. Three clinical trials using this antisense therapy have now been reported [19,81]. In the first, involving patients who had baseline Lp(a) levels of 125–437 nmol/L, IONIS-APO(a)_{RX} reduced mean Lp(a) reductions by 66.8% (SD 20.6). In the second cohort of patients, with Lp(a) \geq 438 nmol/L, there was a 71.6% reduction at 12 weeks.

A recent advance in antisense technology has led to the development of IONIS-APO(a)-L_{RX}, a ligand-conjugated antisense oligonucleotide designed to be highly and selectively taken up by hepatocytes. In a phase 1/2a first-in-man study, this molecule achieved a mean reduction in serum Lp(a) of 92% at 36 days. A phase 2 clinical trial in patients with Lp(a) \geq ~150 nmol/L (60 mg/dl) and established CVD completed in November 2018 (NCT03070782). An siRNA-based therapy targeting *LPA* RNA is also in early development phase (NCT03626662).

Statement 8. The management of patients with raised lipoprotein(a) levels (> 90 nmol/L) should include:

- a. Reducing overall atherosclerotic risk
- b. Controlling hyperlipidemia
- c. Consideration of lipoprotein apheresis as per the HEART UK Lipoprotein apheresis statement [58].

8. Targets

In patients with raised Lp(a), standard algorithms used in risk calculators such as the ACC/AHA Pooled Cohort Equations [82], Systemic Coronary Risk Evaluation (SCORE) [7] and QRISK[®]3–2017 [83] may underestimate cardiovascular risk. In the absence of randomised, controlled trial data demonstrating reduced CV risk with reduction in Lp(a), it is not possible to suggest a desirable target for Lp(a). Instead, in patients with a raised serum Lp(a) > 90 nmol/L, we recommend multiple risk factor intervention to reduce atherosclerotic risk. This should include achievement of greater than 50% reduction in non-HDL-C as the priority to reduce cardiovascular risk, with high intensity statins as the first line medication. The alternative, absolute non-HDL-C target of < 100 mg/dl (2.5 mmol/L) as recommended by JBS3 [84] is approximately equivalent to LDL-cholesterol < 70 mg/dl (1.8 mmol/L) as per the 2016 ESC/EAS guideline [7]. In patients with progressive CVD and a history of recurrent events despite maximum tolerated lipid lowering therapy, including PCSK9 inhibitors, consideration should be given to lipoprotein apheresis if Lp(a) is above 150 nmol/L.

Although both LDL-C (and non-HDL-C) measurements contain a contribution from Lp(a) cholesterol which could potentially lead to overestimation of LDL-C, correction factors for non-HDL-C and LDL-C to exclude Lp(a) associated cholesterol are 1) not validated with isoform independent assays in treated and untreated patients 2) not validated in large epidemiological studies for CV risk prediction or in RCTs of lipid lowering therapies and 3) not in clinical use. Therefore, correction for Lp(a) cholesterol is not currently recommended. Nevertheless, it should be recognized, that the contribution of Lp(a) to LDL-C and non-HDL-C may be substantial. Expression of Lp(a) in molar units allows appreciation of its concentration relative to apo B expressed in molar units.

Statement 9. In patients with raised Lipoprotein(a) levels (> 90 nmol/L), desirable non-HDL-cholesterol is < 100 mg/dl (2.5 mmol/L).

9. Future research

Commercial assays for Lp(a) do not use antibodies that are isoform independent. The development of such an antibody on a commercial scale would considerably improve consistency between assays. The National Heart, Lung, and Blood Institute have recently published recommendations to facilitate basic, preclinical and clinical research on Lp(a) [10]. In our opinion, research evidence is required in three key areas in order to guide the management of Lp(a) associated CV risk. Firstly, interventions that can selectively lower Lp(a), such as Lp(a) apheresis and antisense oligonucleotides to *LPA* RNA, should be tested in randomised, controlled clinical trials to evaluate their effect on CVD outcomes. These should be performed for both primary and secondary prevention, as well as in specific disease states, such as FH and calcific aortic valve stenosis. Clinical trials in secondary prevention should be a priority and if successful, will allow health economic analysis to be performed. The inclusion criterion threshold level of Lp(a) in these outcome studies will need to be carefully chosen, possibly around ~150 nmol/L, the current threshold for apheresis in Germany [85]. Second, the role of antiplatelet therapy for primary prevention in patients with elevated Lp(a) needs to be clarified in prospective randomised, controlled clinical trials. Finally, studies in global multi-ethnic populations have highlighted pronounced differences in Lp(a) levels across ethnicities. Ethnicity is a key variable in assigning cut-off values of Lp(a) for cardiovascular risk prediction. Further epidemiological studies of specific ethnic groups are required to establish clinically relevant Lp(a) cut-off values.

Statement 10. Future work needs to focus on:

- a. Development of commercial truly isoform insensitive assays
- b. Randomised, controlled interventional studies that selectively lower Lipoprotein(a) in primary and secondary prevention of ASCVD
- c. The role of antiplatelet therapy in primary prevention in patients with elevated Lipoprotein(a)
- d. Lipoprotein(a) reference ranges in different ethnic groups.

Search strategy and selection criteria

Data for this Review were identified by searches of Web of Science, PubMed, and references from relevant articles using the search terms “Lipoprotein(a)”, “Lp(a)”, and “cardiovascular risk”.

The HEART UK Medical, Scientific and Research Committee had 2 meetings regarding the consensus paper. The first meeting critically reviewed the literature and agreed the ten statements to be included. The second meeting examined the first draft of the consensus paper. JC and RDGN compiled the first draft. All committee members contributed to revision of the manuscript.

Declaration of competing interest

Several of the Consensus Panel members have received lecture honoraria, consultancy fees, and/or research funding from Akcea (RDGN, DD, HS). The remaining authors have nothing to disclose.

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