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How should public health recommendations address Lp(a) measurement, a causative risk factor for cardiovascular disease (CVD)?

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ABSTRACT

Background and aims: Elevated concentrations of Lipoprotein (a) [Lp(a)] is an inherited, causal risk factor for atherosclerotic cardiovascular disease (ASCVD). This study aims to investigate the clinical utility for patients, and the economic benefit to healthcare systems and society of measuring Lp(a) concentrations more widely today.

Methods: We conducted a structured literature review to identify the economic and health benefits and costs of measuring the Lp(a) concentration, potential barriers hindering the uptake of the measure, and potential solutions to address them. These findings were then discussed in an advisory board attended by experts and patient organisations.

Results: It was found that if Lp(a) concentration is measured more widely today, patients, healthcare system and society would experience clinical and economic benefits even before specific Lp(a) lowering pharmacological treatments become available. Furthermore, a wider uptake of the Lp(a) measurement would support the development of epidemiological data.

Conclusions: For Lp(a) measurement to be more widely used, key barriers which are hindering its uptake need to be addressed. These include i) the perception that the measure may have limited clinical value, ii) lack of awareness on Lp(a), iii) lack of data on the CV benefit of reducing Lp(a), iv) technical and clinical guidelines barriers, and v) healthcare system barriers. Scientific communities and industry should collaborate to address technical challenges and deficiencies in clinical guidelines. However, policy intervention will be crucial for national ASCVD plans to acknowledge the importance of Lp(a).

1. Introduction

1.1. Background

Despite the considerable progress in the science and the medical research in the cardiovascular space, cardiovascular diseases (CVDs) are still the number one cause of death globally, taking an estimated 17.9 million lives each year (which is 31% of all deaths worldwide) [1]. In particular, atherosclerotic cardiovascular disease (ASCVD) is the most prevalent form of CVD [2]. There are many factors that increase the risk of ASCVD (e.g. fatty animal-rich diet, smoking, diabetes mellitus, obesity, inactive lifestyle, hypertension) and hyperlipidaemia is the major cause of different types of ASCVD (HEART UK guideline [3]; ESC/EAS guidelines [4]), including coronary heart disease (CHD), ischemic cerebrovascular disease, and peripheral arterial disease (PAD) [4,5]. In many circumstances, hyperlipidaemia is easily treatable and

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there exist several guidelines for its management, however, in certain cases treatment is challenging [3,6,7].

1.2. Lp(a) is an independent, inherited, causal risk factor for ASCVD

Elevated Lipoprotein (a) [Lp(a)] concentrations, defined as greater than the 80th centile, i.e. Lp(a) concentrations above 50mg/dL or ~105nmol/L, is an inherited risk factor for ASCVD and the most common form of hyperlipidaemia. For example, one study estimated that having Lp(a) values > 100nmol/L (48mg/dL) accounts for 5.7% of CVD events in the patient cohort [8]. In particular, elevated level of Lp(a) is estimated to affect 10%–30% of the population (approximately 1.42 billion people globally) [9–11].

1.3. Measurement of Lp(a)

This can be used to identify individuals with very high inherited Lp (a) plasma levels and familial risk, to reclassify people who are borderline between moderate and high-risk, and to optimize management and treatment of other CVD risk factors in order to reduce the overall risk. Overall, European societies and many individual European countries in addition (e.g., in France, Germany, and the UK) have developed clinical guidelines recommending the measurement of Lp(a) (Table 1). The Canadian guidelines also recommend that Lp(a) should be measured once in a patient's lifetime, as part of initial lipid screening to assess cardiovascular risk [12].

In general, there is alignment between these guidelines, with all of them recommending Lp(a) measurement as a routine part of clinical assessment in high-risk individuals, but some now recommend measurement at least once in the lifetime of all individuals (during a stable phase in the patient's life), given that the Lp(a) concentration remains largely stable throughout life [14]. However, given that there are non-genetic factors that may affect the Lp(a) measurement, such as acute-phase reactions and renal disease, there may be the need for repeat Lp(a) measurement in selected cases. Interestingly, as advancement in medical research have clarified the role of Lp(a), guidelines have undergone frequent updates to reflect the latest scientific findings. For example, the 2016 European ESC/EAS guidelines were updated in 2019 to extend measuring Lp(a) concentration in all individuals (and not only to selected cases, as recommended previously). Additionally, the French clinical guidelines published by the French Society of Cardiology in 2021 (in anticipation of coming specific pharmacological treatments) now state that elevated Lp(a) is, amongst other risks, associated with an increased risk of myocardial infarction (MI) [13].

1.4. Challenges with the Lp(a) concentration measure

Despite the clinical recommendations, the uptake of the measurement of Lp(a) concentration is limited across markets, and this is partially driven by the current lack of pharmaceutical treatment specifically indicated to treat elevated Lp(a), which is perceived as a limitation to effectively prevent ASCVD risks [4]. In particular, decision makers and physicians may have a perception that there is limited value of including Lp(a) measurement in lipid panels. Additionally, there exist other barriers, such as reimbursement hurdles, that may be limiting the wider uptake of Lp(a) measurement.

1.5. Objectives of this study

In this context, this study aims to address three topics. First, as specific pharmacological treatments for elevated Lp(a) are still at the development stage, we investigate whether there is any clinical utility for the patients, or economic value for the healthcare systems and the society, of measuring the Lp(a) concentration more widely today. Second, in addition to the perceived lack of value, we research what other barriers may limit the uptake of the measurement of Lp(a) concentration. Third, we would like to provide policy recommendations that would help addressing those barriers.

2. Methods

To answer the research questions, we have undertaken a two-step analysis. In the first step we conducted a structured literature review to identify the benefits and costs of measuring the Lp(a) concentration, the potential barriers to the uptake of the measure, and the potential solutions to address them. We used Scholar Google and PubMed as search engines to research publications from 2016 to 2020 and the authors have selected the highest relevant and most impactful publications

Table 1
A comparison of the clinical guidelines available in Europe, France, Germany, UK [3,4,12,13].

Region or country	Europe	France	Germany	UK	Canada
Year of publication	**2019**	**2019 (refers to ESC/EAS)**	**2019 (refers to ESC/EAS)**	**2019**	**2021**
Recommend measuring Lp (a)?	✓	✓	✓	✓	✓
Purpose of measure	Identify individuals with very high inherited Lp(a) concentrations and for reclassification in people who are borderline between moderate and high-risk	Identify individuals with very high inherited Lp(a) concentrations and for reclassification in people who are borderline between moderate and high-risk	Identify individuals with very high inherited Lp(a) concentrations and for reclassification in people who are borderline between moderate and high-risk	To optimize management and treatment of other CVD risk factors Identify familial risk	Identify individuals with very high inherited Lp(a) concentrations
Patient population in whom to measure	All individuals	Familiar hypercholesterolemia and other diseases	All individuals	Family history of premature ASCVD; First-degree relatives with raised Lp(a); Familial hypercholesterolemia; Calcific aortic valve stenosis; CVD risk	All individuals
High risk Lp(a) level	>50 mg/dL or ~100–125 nmol/L	>50 mg/dL or ~100–125 nmol/L	>50 mg/dL or ~100–125 nmol/L	32–90 nmol/l minor; 90–200 nmol/l moderate; 200–400 nmol/l high; >400 nmol/l very high	≥50 mg/dL or ≥ 100 nmol/L
Frequency of measure	At least once	At least once	At least once	Once	Once

in English on the topic of "Lp(a)", "risk factor" and "ASCVD". To capture specific information (e.g., clinical guidelines, the prevalence of elevated measure of Lp(a) concentration, reimbursement status and cost of an Lp (a) test across markets of interest), additional publications have been hand-searched to identify the state-of-play. A total of 88 publications have been considered for the analysis.

In the second step, we have discussed the findings from the literature review with an advisory board attended by European- and US-based clinical, policy and bioethics experts together with patient organisations from both regions (refer to the Supplementary Table 1 for more details). The advisory board had European-specific and US-specific breakouts session to discuss regional topics. Furthermore, experts were asked to provide written feedback before and after the advisory board on country-specific issues. Subsequently, to support some of the statements made in the advisory board, we also collected the anecdotal evidence from three European patients via anonymous interviews. The patients were identified by FH Europe, the European patients' organisation, which aims to improve Europe-wide awareness, understanding, and access to diagnosis and treatment of inherited lipid conditions - through its patient network. In the interviews, the patients provided the authors details on their patient journey, from diagnosis to treatment, together with any barriers they faced in their journey. While this study reports the findings from the European-specific discussion, a companion study covers the findings specific to the US.

3. Results

3.1. Value to patients, healthcare systems and society of the wider uptake of the Lp(a) concentration measure today

Despite clinical guidelines recommending Lp(a) measurement, a legitimate question decision maker may ask what would be the clinical and economic value of performing the test if specific pharmacological treatments for elevated Lp(a) concentrations are not (yet) available and whether this would justify the cost of the test.

3.1.1. Benefits to patients of measuring Lp(a) concentration

The experts in the advisory board all agreed that there is already an immediate benefit to patients in measuring Lp(a) concentration, even if effective pharmacological treatments are not yet available. In particular, Lp(a) measurement facilitates the identification and better management of patients at a high cardiovascular risk by allowing more accurate risk stratification [15]. For example, patients with very high Lp(a) have a prognosis similar to patients with heterozygous Familial Hypercholesterolemia (FH) [4,16,17]. In particular, knowledge of elevated Lp(a) enables physicians to provide the appropriate preventive care to patients, treatment for the patient's other risk factors which could be treated and perform cascade screening [18]. For example, patients with high Lp(a) concentrations may have less-than expected LDL-C lowering on statin therapy and have greater residual CVD risk despite maximum tolerated treatment with statin and ezetimibe [19]. However, they would derive greater relative benefit from PCSK9 inhibitor therapy, as this may additionally reduce Lp(a) by 15–30%, but the reduction rate is below 20% in patients with high Lp(a) concentrations [20–22]. This could contribute to the reduction of premature CVD events and associated deaths and generate healthcare system savings. Furthermore, individuals who are made aware of their elevated Lp(a) and associated risks may be more empowered to adhere to recommended therapy and adopt beneficial changes in their lifestyle habits to decrease the overall CVD risk associated with other modifiable risk factors [21].

Moreover, given that Lp(a) is transmitted in an autosomal dominant pattern, close relatives of individuals with elevated Lp(a) could potentially be identified through cascade screening, and, if needed, treated earlier in their lives [23]. For example, the HEART UK guideline recommends that amongst other targeted patient populations, patients with a first-degree relative with raised Lp(a) should have their Lp(a) concentration measured [3]. Additionally, the earlier identification of such patients can enable physicians to engage earlier with these patients and thus will serve to increase awareness of the fact that elevated Lp(a) is an inherited cause of premature ASCVD.

3.1.2. Healthcare system benefits

European payers may question whether these clinical benefits compensate the cost of the test. In general, the cost per test for a public payer is estimated to be comparative to the standard lipid panel that includes estimates of other lipoprotein subfractions, and lower than the FH genetic test. In the UK, measurement of Lp(a) concentration does not have a unique tariff that is used for purposes of reimbursement, but it is estimated that the cost to run a single Lp(a) measure varies from £2 (€2.3) to £25 (€29.1) [24]. In comparison, the cost of measuring the full blood count is £6.00 (€7); the cost of measuring blood glucose (HbA1c) is £6.42 (€7.5); the cost of calcium scoring is £71 (€82.8); and the cost of each FH index case testing is ~£280 (€326.5) and for a cascade screening test is £75 (€87.5) [25–27]. In Germany, laboratories can charge a maximum value of €11.90 for measuring the Lp(a) concentration in the outpatient setting whereas the cost to the hospital is around €5 per test in the inpatient setting [28,29]. In comparison, the cost of measuring the total cholesterol, triglycerides, HDL cholesterol and LDL cholesterol is € 0.25 each; and the cost of the cascade FH test is €70.81 [30,31]. However, these costs are not comprehensive; for example, these values do not include the cost associated with sample collection, laboratory service delivery and reporting – but these costs would be less per measure if various measures are requested simultaneously. Additionally, when the Lp(a) concentration is measured by automated analysers in conjunction with cholesterol measures, the cost of the measure is significantly lower than that reported above. Despite this, given the overall economic burden of CVD, the cost of the test appears reasonable and, based on the available evidence, measuring Lp(a) concentration may in fact be cost-effective [23] and potentially cost-saving, particularly because recommendations only call for measuring Lp(a) concentration once in a patient's life for screening or diagnostic purposes and it could be done as part of an initial lipid screening to assess CVD risk. Moreover, given that high CVD mortality is associated with considerable monetary costs, with the total economic toll of CVD estimated at €210 billion a year (2017) in Europe [32], even a small clinical benefit would likely result in cost savings for the healthcare system (Table 2).

In particular, wider access to Lp(a) measurement could improve the targeting of lipid lowering treatment and other preventive therapies, leading to a reduction in hospital admissions. This would result in an improved risk stratification of patients and better management of CVD patients by providing optimal medical treatment [18]. Additionally, wider access to the measure can reduce the need for FH testing amongst patients with elevated Lp(a) concentration. For instance, one clinical study estimated that 4.4% of patients admitted to a coronary care unit had both elevated Lp(a) and phenotypic FH, demonstrating its frequency [16]. Thus, Lp(a) measurement has the potential of making healthcare systems more resilient and well-prepared for instances of patient influx that could otherwise impact hospital care quality (as was observed

Table 2
Estimates of annual CVD cost per year across a sample of European countries.

Estimates of annual CVD cost per year, CVD cost per capita per year, and as a percentage of total health expenditure			
France	€15.1 billion (2013) [33]	€224.1/capita (2013) [33]	8.4%
Germany	€46.4 billion (2015) [34]	€557.4/capita (2015) [34]	15.0%
Italy	€4.0 billion (2014) [35]	€67.2/capita (2014) [35]	2.5%
Spain	€1.7 billion (2014) [35]	€35.9/capita (2014) [35]	1.6%
UK	€18.4 billion (2019) [36]	€273.7/capita (2019) [36]	10.1%

Note: The CVD cost per capita per year was estimated by dividing the annual CVD cost per year provided in references [33–36] by each of the respective countries' populations. The references do not necessarily utilise the same methodology in estimating the annual CVD cost per year.

Table 3
An overview of the key barriers that are hindering the uptake of the measure of Lp(a) concentration in Europe.

An overview of the key barriers that are hindering the uptake of the measure of Lp(a) concentration in Europe
Limited perception of value and lack of awareness of CVD risk: Physicians may have a limited perception of the clinical utility of the Lp(a) test due to there not being a therapeutic option for high Lp(a) available yet [43], whilst patients may lack awareness of family history of ASCVD or of elevated Lp(a) concentrations
Technical and clinical guidelines barriers: A key technical barrier to the measure of Lp(a) concentration is the lack of standardised assays on commercial platforms and the utilisation of different units to measure Lp(a) [23]. Furthermore, there is a lack of statements of measuring Lp(a) in some clinical guidelines and a lack of clear and actionable recommendations in clinical guidelines on how physicians should manage a patient with elevated Lp(a) [44]].
Healthcare system barriers. Limited reimbursement of the Lp(a) concentration measure and spending control measures act as a barrier to the uptake of the measure. Additionally, in some countries, there are only relatively few laboratories currently providing an Lp(a), assay, which serves as a barrier to sample flow.

during the COVID-19 pandemic).

Finally, it is estimated that for patients with Lp(a) concentrations above 175nmol/L who are receiving experimental products in the currently ongoing trials, the annual CVD incidence could potentially be reduced by at least 20%, and this would translate into healthcare savings [8].

3.1.3. Other benefits of measuring Lp(a) concentration

In addition to the clinical and healthcare system benefits, experts in the advisory board have identified three other reasons why uptake of the measurement of Lp(a) concentration should be undertaken now even if a specific treatment is not yet available.

First, there are already specific treatments in the development phase that may reach patients in the next three or four years and deliver significant health benefits. By the time these treatments will enter the market, eligible patients could already have been identified to maximise the benefits of these specific treatments and avoid the health impact of delayed diagnosis. This supports the view that barriers limiting the uptake of the Lp(a) concentration measure should be addressed in a timely manner. Generally, policy interventions take time to be implemented and to translate into changes in the clinical practice. Thus, the sooner that policies are implemented to ensure that measurement of Lp (a) concentrations are available to all individuals, as recommended in the 2019 ESC/EAS clinical guidelines, the sooner those likely to benefit will have access to appropriate treatment.

Second, a wider uptake of the measure of Lp(a) concentration would support the collection of up-to-date epidemiological data needed in healthcare planning and decision making. With more widespread measurement, there will be increased real-world evidence of the prevalence of elevated Lp(a) concentrations, which can contribute to the refinement of the cardiovascular risk assessment and management, and the development of more accurate risk level thresholds [3]. An improved understanding of the prevalence of patients with elevated Lp(a) would also help inform prioritisation of certain healthcare policies regarding measuring Lp(a) concentration and treatment guidelines, whilst encouraging patient advocacy groups to conduct targeted educational campaigns. For instance, information on CVD risk has been used by policymakers to develop primary prevention strategies for reducing overall CVD risk and to reduce socioeconomic inequalities in health, and to guide the implementation of testing programmes [37].

Third, interventions to support the uptake of the Lp(a) measurement today can help reducing healthcare inequalities. Socioeconomic disparities are prominent in CVD: patients with a lower socioeconomic status (SES) or lower educational level demonstrate an increased mortality rate compared to high SES patients [38]. For example, a UK-based study found that CVD patients who have a lower SES had higher numbers of comorbidities, with one-fifth of patients in the most deprived fifth having 5 or more comorbidities [39]. Patients with a lower SES may be less likely to request physicians for an Lp(a) test, particularly if they are required to pay for the test themselves, whilst physicians may unconsciously request fewer Lp(a) tests for patients with lower SES as they may believe that low SES patients will comply less with provided medical advice and less likely to return for follow-up visits [40]. Thus, if the measure of Lp(a) concentration is reimbursed and ideally available to all adults, there would be fewer discrepancies in the uptake of the test across socioeconomic groups and provide equality of access of the test across different parts of the country. Furthermore, as there are disparities in prevalence of elevated Lp(a) across different ethnic groups, Lp(a) measurement may contribute to reducing inequities in CVD care related to ethnicity. Evidence demonstrates that highly elevated Lp(a) mediates risk irrespective of race, and that patients who are above the 80th percentile for their race are at increased risk [41].

3.2. Challenges to the uptake of the of Lp(a) measurement

Despite clinical guidelines recommending the measurement of Lp(a) concentration and the immediate benefits for the patients and the society, the uptake of the testing still remains limited in European countries [42]. The literature identifies a number of challenges that hinder testing uptake. According to the experts in the advisory board, some of these challenges – which are summarised in Table 3 - should be considered priorities to be addressed. Although the limited perception of value and lack of awareness of Lp(a) is prevalent across countries, the technical, clinical guidelines and healthcare system barriers are key barriers that need to be prioritised in order to facilitate the uptake of the Lp(a) concentration measure.

3.2.1. Limited value perception and lack of awareness

A common misconception among clinicians regarding Lp(a), which might partially drive the clinical inertia and lack of testing, is the perceived lack of therapeutic options for an individual with high Lp(a) [43]. Additionally, patient unawareness of family history of ASCVD or Lp(a) concentrations may cause also physicians to overlook the measure of Lp(a) concentration as an appropriate proactive screening option. The advisory board highlighted that physicians in Germany are unwilling to request an Lp(a) test due to the lack of an available specific pharmacological therapy for elevated Lp(a) and due to the misconception that management of such patients cannot be improved if they were to be identified. Similarly, given that measuring Lp(a) in the UK is at the physician's discretion, the measure is only occasionally requested by specialist physicians and is not routinely done in general practice [45]. Value perception was also regarded as a barrier to the uptake of the measure of Lp(a) concentration in France, and the measure is not systematically used in France to detect lipid abnormalities [46]. Furthermore, while guidelines and recommendations for measuring Lp(a) concentration in ASCVD patients exist and are made publicly available, through organisations such as ESC/EAS, some physicians, especially providers who are not lipid specialists, demonstrated a lack of awareness of the formal guidelines and the appropriate clinical triggers for Lp(a) measurement [14]. For example, in the advisory board it was highlighted that some physician groups, such as cardiologists and diabetologists, in the UK have limited awareness of the test. Additionally, physicians who are aware of the formal guidelines at times do not adhere to their recommendations. The European patients interviewed have also reported these issues.

3.2.2. Technical and clinical guidelines barriers

Overall, there exist many excellent assays to measure Lp(a) accurately. However, a key technical barrier to measuring Lp(a) concentration is the lack of standardisation of assays. Difficulties in the

standardization of Lp(a) measurements are due to different analytical methods, each with its own margin of error, that are currently in use to measure Lp(a) concentration [47]. Some of these technical issues relate to choice of assay calibrators and the assignment of appropriate target values to these, reporting of Lp(a) mass (typically mg/dL) versus particle number (nmol/L), measurement of Lp(a) in one unit but reporting it in another unit, lack of familiarity with both unit measures amongst physicians who are not working with Lp(a) daily, and finally an absence of implemented guidelines for validation of methodical approaches [23]. In addition, the lack of statements regarding the utility of measuring Lp (a) concentration in some clinical guidelines and the lack of clear and actionable recommendations on how physicians should manage a patient with elevated Lp(a) in clinical guidelines, result in insufficient and uneven uptake of the measure [44]. For instance, in the UK there are geographical discrepancies in access to the measure of Lp(a) concentration and this is partially attributed to the absence of guidelines by The National Institute for Health and Care Excellence (NICE) on Lp(a) and to the fact that neither the NICE familial hypercholesterolaemia guideline (CG71, 2017) nor the Lipid Modification and Risk Assessment Guideline (CG181, 2014) make any mention of, nor recommend measuring Lp(a) [48,49]. One reason why NICE did not incorporate measuring Lp(a) in these guidelines was due to the lack of published cost-effectiveness studies demonstrating the value of Lp(a) measurement and such studies are required for the measure to be integrated into NICE guidelines. Another technical barrier is that various thresholds to define high Lp(a) concentrations have been used across different guidelines, and in most cases the thresholds have been converted to derive both sets of units, against recommendations, giving rise to discrepant values. For example, the European Atherosclerosis Society Consensus Panel chose an Lp(a) threshold of ≥50 mg/dl (or ≥105 nmol/L), the German guidelines use an Lp(a) threshold >60mg/dl (>120nmol/l), whereas the US used ≥30 mg/dl (or ≥75 nmol/L) as the risk threshold until 2018 [9, 50]. These different thresholds cause difficulties in interpreting the result and are likely to reduce physicians' enthusiasm for requesting the measurement.

3.2.3. Healthcare system barriers

Limited reimbursement of the measure of Lp(a) concentration and spending control measures act as a barrier to the measure. For example, in France Lp(a) tests are not reimbursed in the community setting, while in Germany physicians may be reluctant to request an Lp(a) test due to control measures in place to prevent over-spending on testing [51]. Although in Germany testing of Lp(a) concentrations is recommended (but not required) as part of the FH diagnosis, the test has low uptake among cardiologists assessing patients for FH [52]. Additionally, the fact that practitioners have a fixed laboratory budget serves as a barrier to the broader reimbursement of the measure. In both France and Germany, patients frequently pay for the test out of their pocket and thus the cost of the test is perceived as a key barrier. Despite that the Lp(a) concentration measure is routinely available through automated analysers, another country-level barrier to Lp(a) measurement is that in some countries only a few laboratories are currently measuring Lp(a), resulting in the need for hospitals and clinics to outsource the measurement of Lp(a) concentration. For example, in the UK the majority of Lp(a) test volume is processed by a core set of 15–20 labs, as its low volume does not justify local in-house processing for most hospitals and private labs [24]. As a result, this can lead to delay in turnaround time and increased costs.

3.2.4. Other barriers

The literature identifies other barriers that can limit the uptake of the measurement of Lp(a) concentration, however the experts in the advisory board perceived these as second order barriers. For instance, the fact that the measure of Lp(a) concentration cannot be easily found in some of the paper and electronic forms used by physicians, primarily in the primary care setting, to request the test were not considered as a key barrier to uptake, nor the fact that electronic healthcare systems do not alert physicians to request the Lp(a) measurement [24]. Furthermore, the lack of patients' awareness on Lp(a) and familial risk was not perceived as a key barrier to the measure of Lp(a) concentration, as this could be counteracted by the physicians' awareness [53]. Experts also did not consider that the current amount of personnel with enough technical expertise on the Lp(a) measure is hindering its uptake [53]. Finally, the experts from European countries did not perceive that there is a lack of political support to increase the measure of Lp(a) concentration, instead, noting that decision-makers have not yet prioritised the measure due to them not being aware of Lp(a) and of the value of measuring it.

3.3. European patient experiences with diagnosing and managing elevated Lp(a) concentration levels

The challenges to the uptake of the Lp(a) measurement and the value of the Lp(a) concentration measure to patients were echoed by three

Table 4
European patient feedback on the need to raise awareness and to utilise the Lp(a) concentration measure as a tool to manage other CVD risk factors.

European patient feedback based on their patient journey	
The need to raise awareness on measurement of Lp(a) levels	*"Awareness raising of Lp(a) within the Healthcare Professionals community is vital. We do not present in the traditional cardiac case way. When we do it can be too late. We often appear fit and healthy on the surface."* *"The cardiologist identified that the way I had presented was highly unusual and that I was a very near miss. He commented on my luck and that I should be dead."* *"It took almost* 12 months *from presenting originally with my GP to beginning to address my Lp(a) diagnosis. So elapsed time was a big factor. This is a huge mental burden. Also my initial presentation was not taken seriously enough. My conviction that something was not right […] literally saved my life. […] I am sure I would not be here without it."*
Lack of awareness about guidelines on Lp(a) measurement	*"I was 49 years old when out of the blue I had a heart attack. During all the tests that followed, most of the traditional risk factors seemed to be ok. Blood pressure, cholesterol and blood sugar levels were all fine, I am a non-smoker and not very stressed. Although I am overweighed, I was told that this risk factor alone could not cause that many problems at such a relatively young age.* *Six months later, again one of my coronary arteries was almost fully blocked and it showed this was caused by an inflammation. Therefore, the levels of statins I was already prescribed before, were doubled. In a few months I developed an intolerance against this medicine and became very ill, both physically as mentally. I was prescribed a PCSK9 inhibitor, but this had not enough impact on my cholesterol levels. This was the reason why my cardiologist referred me to a vascular internist, who tested my blood very extensively and, amongst others, also my Lp(a) level."*
Management of other risk factors	*"I was briefed on my condition and its implications, then I was given medication for the treatment of my other cardiovascular disease (CVD) risk factors, such as high LDL cholesterol and high blood pressure, in order to reduce my overall CVD risk. The aim was to reduce my LDL cholesterol to a very low level (< 1.4* mmol/L*), which is being achieved by a treatment consisting of PCSK9 inhibitors, in addition to statins and ezetimibe."* *"From a patient's point of view, Lp(a) measuring is of very high value, as your doctor can help you to reduce your other risk factors, such as high LDL cholesterol and high blood pressure, in order to lower your overall CVD risk. Awareness of elevated Lp(a) is all the more important as for instance your LDL level will need to be lower than for patients without elevated Lp(a)."*

Table 5
Five potential solutions to address the varied barriers to measuring Lp(a) concentration in Europe.

An overview of potential solutions to address the varied barriers to measuring Lp(a) concentration in Europe	
Solutions to the value perception and lack of awareness barriers	1. Educational campaigns targeting physicians and patients on Lp(a) and its role in ASCVD. 2. Increased dissemination and socialisation activities of recent guidelines on measuring Lp(a) concentration.
Solutions to the technical and clinical guidelines barriers	3. Scientific committees and the industry should collaborate in the standardisation and validation of Lp(a) assays. 4. Clinical guidelines should be updated to cover Lp(a) and incorporate clear and actionable recommendations for patients with elevated Lp(a).
Solutions to the healthcare system barriers	5. More studies demonstrating the benefits of measuring Lp(a) concentration are needed to increase policymaker's awareness, focus and prioritisation of the issue.

European patients who provided the authors with an overview of their patient journey, including the hurdles in being diagnosed with elevated Lp(a) concentration and how the diagnosis improved the management of their other CVD risk factors (Table 4).

4. Discussion

4.1. Policy recommendations to support a wider uptake of Lp(a) measurement

Experts in the advisory board agreed that there is a need for stronger political leadership to increase the uptake of Lp(a) measurement in order to reduce ASCVD risk and prevalence. Policy intervention is needed now to address the value perception and lack of awareness, technical, clinical guidelines, and healthcare system barriers of measuring Lp(a) concentration (Table 5).

4.1.1. Solutions to the value perception and lack of awareness barriers

Educational campaigns targeting physicians on the clinical and healthcare benefits of measuring Lp(a) concentration are needed to address misconceptions around the measure, for example through the publication of consensus statements by patient organisations (such as HEART UK's consensus statement on Lipoprotein(a)) [3]. In addition to educating physicians, the public needs to be educated on the role of Lp (a) in ASCVD. Moreover, such campaigns should cover recent guidelines on measuring Lp(a) concentration to identify high risk patients [53]. Finally, more efforts need to be made to provide continuity between the provision of different guidelines on the measurement of Lp(a) concentration. For example, national European clinical guidelines could reference the latest ESC/EAS Guidelines for the management of dyslipidaemias [4].

4.1.2. Solutions to the technical barriers

Scientific committees and the industry should collaborate in the standardisation and validation of Lp(a) tests to ensure that all patients have access to good quality tests, and the regulators should ensure that the Lp(a) assays on the market are appropriately standardised. In particular, scientific communities should promote Lp(a) being measured in nmol/L rather than in mg/dL in conjunction with driving the availability of nmol/L assays to measure Lp(a) concentration. For instance, HEART UK recommends that results should be expressed in nmol/l of Lp (a) particles and that conversion of mass units to molar units or vice versa introduces inaccuracy and should be discouraged [3]. Such collaborations should build on World Health Organisation's (WHO) protocols for standardisation of Lp(a) assays published in 2003, which have contributed to more reliable quantification, reduced the bias caused by isoform size of Lp(a), and have made within study comparisons more robust [3]. The European Federation of Laboratory Medicine (EFLM), the International Federation of Clinical Chemistry (IFCC) and the Northwest Lipid Research Laboratories in the US are working towards the standardisation of Lp(a) assays across different suppliers. In the meantime, organisations can recommend which of the Lp(a) tests are recommended for use. For example, HEART UK has published a statement that only assays based on Denka reagents with calibrators traceable in nmol/L to WHO/IFCC reference material can be recommended [3]. However, more manufacturers should be incentivised to develop Lp (a) assays for their platforms, in order to make the Lp(a) measurements more accessible.

Furthermore, clinical guidelines for the management and prevention of CVD need to be updated to cover Lp(a) and incorporate clear and actionable recommendations for patients with elevated Lp(a) and recommend cascade screening to be able to provide early CVD preventive measures to individuals with elevated Lp(a) concentration measures. In particular, the Lp(a) measurement would be more easily incorporated in national recommendations – and the guidelines would be translated into clinical practice – if stakeholders could produce more data demonstrating the cost-effectiveness of the measure or studies showing how many lives can be saved by managing other risk factors if the measure were more widespread. For instance, in the UK for the test to be recommended in the NICE guidelines, there needs to be a cost-effective analysis that demonstrates that test which appears clinically effective is also cost-effective (or cost-saving) for a target patient population.

4.1.3. Solutions to the healthcare system barriers

In Europe, policymakers need to be made aware of the clinical, healthcare and society benefits of measuring the Lp(a) concentration (e.g., more data demonstrating the CVD risk which is attributable to Lp(a) in different populations and data demonstrating that the measure reduces CVD events and health inequalities) through key stakeholders (e.g., physicians societies and patient advocacy). However, for this to be possible, more studies and advocacy demonstrating such benefits are needed. Only once there is understanding of the value of measuring patients for Lp(a) today, there can be an expectation to have a prioritisation of the issue at political level and wider uptake of the test. Once political awareness is raised and Lp(a) is prioritised, political support is expected to overcome the challenges coming from the lack of reimbursement in France or patients being required to pay for the Lp(a) test out of their pocket in Germany. Additionally, policymakers need to ensure that there are enough laboratories that provide Lp(a) measurement. Policymakers can encourage collaboration between the industry, laboratory systems and test manufacturers to make better and cheaper assays more widely available.

4.2. Key conclusions

Elevated Lp(a) concentrations is one of the most important common inherited causes of ASCVD and one study estimated that having Lp(a) values $>$ 100nmol/L accounts for 5.7% of CVD events [8,54]. The 2019 ESC/EAS clinical guidelines recommends Lp(a) as a routine test, ideally in all individuals due to the key benefits that the measure of Lp(a) concertation brings to patients, healthcare systems and society, even without a specific pharmaceutical option to treat it. In particular, the Lp (a) measure can lead to the identification of high-risk individuals and to the better management of patients with elevated Lp(a), which in turn can lead to more resilient healthcare systems.

To achieve these benefits, policy intervention is needed now to address the barriers that limit the uptake of the measurement of Lp(a) concentration, such as value perception and lack of awareness, technical, clinical guidelines, and healthcare system barriers. In particular,

policy intervention is needed for national CVD plans to acknowledge the importance of Lp(a) as a risk factor and for clinical guidelines to be translated into clinical practice, i.e., for healthcare systems to proactively identify patients with elevated Lp(a) and manage them effectively.

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Author contributions

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Declaration of competing interest

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Appendix A. Supplementary data

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References

[1] WHO, Cardiovascular diseases, Accessible at: https://www.who.int/health-topics/cardiovascular-diseases/#tab=tab_1, 2021.
[2] P. Libby, J.E. Buring, L. Badimon, G.K. Hansson, J. Deanfield, M.S. Bittencourt, L. Tokgözoğlu, E.F. Lewis, Atherosclerosis, Nat. Rev. Dis. Prim. 5 (1) (2019) 1–18.
[3] J. Cegla, R.D.G. Neely, M. France, G. Ferns, C.D. Byrne, J. Halcox, D. Datta, N. Capps, C. Shoulders, N. Qureshi, A. Rees, HEART UK consensus statement on Lipoprotein (a): a call to action, Atherosclerosis 291 (2019) 62–70.
[4] F. Mach, C. Baigent, A.L. Catapano, K.C. Koskinas, M. Casula, L. Badimon, M. J. Chapman, G.G. De Backer, V. Delgado, B.A. Ference, I.M. Graham, 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk: the Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS), Eur. Heart J. 41 (1) (2020) 111–188.
[5] J.R. Genzen, Atherosclerotic cardiovascular disease risk markers, Accessible at: https://arupconsult.com/content/cardiovascular-disease-traditional-risk-markers, 2019.
[6] S.M. Grundy, N.J. Stone, A.L. Bailey, C. Beam, K.K. Birtcher, R.S. Blumenthal, L. T. Braun, S. De Ferranti, J. Faiella-Tommasino, D.E. Forman, R. Goldberg, 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: executive summary: a report of the American college of Cardiology/American heart association task force on clinical practice guidelines, J. Am. Coll. Cardiol. 73 (24) (2019) 3168–3209.
[7] F. Mach, C. Baigent, A.L. Catapano, K.C. Koskinas, M. Casula, L. Badimon, M. J. Chapman, G.G. De Backer, V. Delgado, B.A. Ference, I.M. Graham, 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk, Atherosclerosis 290 (2019) 140–205.
[8] P. Welsh, C. Welsh, C.A.C. Celis-Morales, R. Brown, L.D. Ferguson, S. Gray, P. Mark, J. Lewsey, D.M. Lyall, J.M.R. Gill, J. Pell, Lipoprotein (a) and cardiovascular disease: prediction, attributable risk fraction and estimating benefits from novel interventions, Eur. Heart J. 41 (Supplement_2) (2020) ehaa946–2833.
[9] E.A. Enas, B. Varkey, T.S. Dharmarajan, G. Pare, V.K. Bahl, Lipoprotein (a): an independent, genetic, and causal factor for cardiovascular disease and acute myocardial infarction, Indian Heart J. 71 (2) (2019) 99–112.
[10] A.N. Berman, D.W. Biery, C. Ginder, O.L. Hulme, D. Marcusa, O. Leiva, W.Y. Wu, A. Singh, S. Divakaran, J. Hainer, A. Turchin, Study of lipoprotein (a) and its impact on atherosclerotic cardiovascular disease: design and rationale of the mass general Brigham Lp (a) registry, Clin. Cardiol. 43 (11) (2020) 1209–1215.
[11] B.G. Nordestgaard, M.J. Chapman, K. Ray, J. Borén, F. Andreotti, G.F. Watts, H. Ginsberg, P. Amarenco, A. Catapano, O.S. Descamps, E. Fisher, Lipoprotein (a) as a cardiovascular risk factor: current status, Eur. Heart J. 31 (23) (2010) 2844–2853.
[12] G.J. Pearson, G. Thanassoulis, T.J. Anderson, A.R. Barry, P. Couture, N. Dayan, G. A. Francis, J. Genest, J. Grégoire, S.A. Grover, M. Gupta, 2021 Canadian cardiovascular society guidelines for the management of dyslipidemia for the prevention of cardiovascular disease in the adult, Can. J. Cardiol. 32 (11) (2016) 1263–1282.
[13] M. Farnier, M. Zeller, D. Masson, Y. Cottin, Triglycerides and Risk of Atherosclerotic Cardiovascular Disease: an Update, Archives of Cardiovascular Diseases, 2021.
[14] G. Thanassoulis, Screening for high lipoprotein(a), Circulation 139 (12) (2019) 1493–1496.
[15] V. Bláha, Lipoprotein (a)-the cardiovascular risk factor: significance and therapeutic possibilities, Vnitr. Lek. 64 (12) (2019) 1160–1168.
[16] K.L. Ellis, J. Pang, D. Chieng, D.A. Bell, J.R. Burnett, C.J. Schultz, G.S. Hillis, G. F. Watts, Elevated lipoprotein (a) and familial hypercholesterolemia in the coronary care unit: between Scylla and Charybdis, Clin. Cardiol. 41 (3) (2018) 378–384.
[17] A. Wang, A. Richhariya, S.R. Gandra, B. Calimlim, L. Kim, R.G. Quek, R.J. Nordyke, P.P. Toth, Systematic review of low-density lipoprotein cholesterol apheresis for the treatment of familial hypercholesterolemia, J. Am. Heart Assoc. 5 (7) (2016) e003294.
[18] N.P. Shah, Q. Wang, K.E. Wolski, L. Cho, E. McErlean, G. Ruotolo, G. Weerakkody, J.S. Riesmeyer, S.J. Nicholls, A.M. Lincoff, S.E. Nissen, The role of lipoprotein (a) as a marker of residual risk in patients with diabetes and established cardiovascular disease on optimal medical therapy: post hoc analysis of ACCELERATE, Diabetes Care 43 (2) (2020) e22–e24.
[19] D.P. Wilson, T.A. Jacobson, P.H. Jones, M.L. Koschinsky, C.J. McNeal, B. G. Nordestgaard, C.E. Orringer, Use of Lipoprotein (a) in clinical practice: a biomarker whose time has come. A scientific statement from the National Lipid Association, Journal of Clinical Lipidology 13 (3) (2019) 374–392.
[20] V. Blanchard, K. Chemello, T. Hollstein, C.C. Hong-Fong, F. Schumann, T. Grenkowitz, B. Nativel, S. Coassin, M. Croyal, U. Kassner, C. Lamina, The size of apolipoprotein (a) is an independent determinant of the reduction in lipoprotein (a) induced by PCSK9 inhibitors, Cardiovasc. Res. (2021), https://doi.org/10.1093/cvr/cvab24.
[21] M.B. Boffa, M.L. Koschinsky, Proprotein convertase subtilisin/kexin type 9 inhibitors and lipoprotein (a)-mediated risk of atherosclerotic cardiovascular disease: more than meets the eye? Curr. Opin. Lipidol. 30 (6) (2019) 428–437.
[22] P. Grützmacher, B. Öhm, S. Szymczak, C. Dorbath, M. Brzoska, C. Kleinert, Primary and secondary prevention of cardiovascular disease in patients with hyperlipoproteinemia (a), Clinical Research in Cardiology Supplements 12 (1) (2017) 22–26.
[23] A. Saeed, S.S. Virani, Lipoprotein (a) and cardiovascular disease: current state and future directions for an enigmatic lipoprotein, Front Biosci (Landmark Ed) 23 (2018) 1099–1112.
[24] Novartis, Lp(a) Diagnostic Landscape Assessment – US, Germany and UK Readout", 2019.
[25] National Clinical Guideline Centre, Preoperative tests - routine preoperative tests for elective surgery, Accessible at: https://www.nice.org.uk/guidance/ng45/documents/guideline-appendices-13, 2015.
[26] NHS England, Familial Hypercholesterolaemia - CCG collaborative commissioning paper, Accessible at: https://www.england.nhs.uk/london/wp-content/uploads/sites/8/2019/08/3.2.2-West-Midlands-CCG-Collaborative-Commissioning-Paper-Familial-Hypercholesterolaemia-2016.pdf, 2015.

[27] NICE, CADScor system for ruling out coronary artery disease in people with symptoms of stable coronary artery disease, Accessible at: https://www.nice.org.uk/advice/mib174/resources/cadscor-system-for-ruling-out-coronary-artery-disease-in-people-with-symptoms-of-stable-coronary-artery-disease-pdf-2285963637563077, 2019.
[28] EBM, Lipoprotein (a), Accessible at: https://www.kbv.de/tools/ebm/html/32456_2902478142349501717824.html, 2021.
[29] Novartis, Lp(a) biomarker testing and reimbursement landscape assessment - cross country payer research output slides, 2020. Internal market research property of NVS.
[30] LADR, LDL-Cholesterin: so niedrig wie möglich, Accessible at: https://ladr.de/ldl-cholesterin, 2021.
[31] Limbach Gruppe, MVG Stoffwechsel Anforderungen, Accessible at: https://www.labor-gaertner.de/fileadmin/user_upload/Dokumente/pdf/Aktuelles/201508_MVG_Stoffwechsel_Anforderungen.pdf, 2015.
[32] E.J. Benjamin, P. Muntner, A. Alonso, M.S. Bittencourt, C.W. Callaway, A. P. Carson, A.M. Chamberlain, A.R. Chang, S. Cheng, S.R. Das, F.N. Delling, Heart disease and stroke statistics—2019 update: a report from the American Heart Association, Circulation 139 (10) (2019) e56–e528.
[33] P. Tuppin, S. Rivière, A. Rigault, S. Tala, J. Drouin, L. Pestel, P. Denis, C. Gastaldi-Ménager, C. Gissot, Y. Juillière, A. Fagot-Campagna, Prevalence and economic burden of cardiovascular diseases in France in 2013 according to the national health insurance scheme database, Archives of Cardiovascular Diseases 109 (6–7) (2016) 399–411.
[34] DE STATIS, Cardiovascular diseases cause highest costs - press release No. 347 of 29 September 2017, Accessible at: https://www.destatis.de/EN/Press/2017/09/PE17_347_236.html, 2017.
[35] Centre for Economics and Business Research (CEBR), The economic cost of cardiovascular disease from 2014-2020 in six European economies, Accessible at: https://www.sanita24.ilsole24ore.com/pdf2010/Sanita2/_Oggetti_Correlati/Documenti/Dibattiti-e-Idee/3Cebr%20-%20The%20economic%20cost%20of%20cardiovascular%20disease%20from%202014-2020%20in%20six%20European%20economies.pdf?uuid=AbV1x4QK, 2014.
[36] Public Health England, Health matters: preventing cardiovascular disease, Accessible at: https://www.england.nhs.uk/blog/the-long-term-plan-is-a-game-changer/, 2019.
[37] C. Kypridemos, K. Allen, G.L. Hickey, M. Guzman-Castillo, P. Bandosz, I. Buchan, S. Capewell, M. O'Flaherty, Cardiovascular screening to reduce the burden from cardiovascular disease: microsimulation study to quantify policy options, BMJ 353 (2016).
[38] J.P. Mackenbach, A.E.J.M. Cavelaars, A.E. Kunst, F. Groenhof, Socioeconomic inequalities in cardiovascular disease mortality. An international study, Eur. Heart J. 21 (14) (2000) 1141–1151.
[39] J. Tran, R. Norton, N. Conrad, F. Rahimian, D. Canoy, M. Nazarzadeh, K. Rahimi, Patterns and temporal trends of comorbidity among adult patients with incident cardiovascular disease in the UK between 2000 and 2014: a population-based cohort study, PLoS Med. 15 (3) (2018) e1002513.
[40] N.C. Arpey, A.H. Gaglioti, M.E. Rosenbaum, How socioeconomic status affects patient perceptions of health care: a qualitative study, Journal of Primary Care & Community Health 8 (3) (2017) 169–175.
[41] S. Varvel, J.P. McConnell, S. Tsimikas, Prevalence of elevated Lp (a) mass levels and patient thresholds in 532 359 patients in the United States, Arterioscler. Thromb. Vasc. Biol. 36 (11) (2016) 2239–2245.
[42] EAS, Commentary: novel therapeutics specific to lipoprotein(a), Accessible at: https://www.eas-society.org/page/Lpa, 2019.
[43] R. Alonso, L.P. de Isla, O. Muñiz-Grijalvo, P. Mata, Barriers to early diagnosis and treatment of familial hypercholesterolemia: current perspectives on improving patient care, Vasc. Health Risk Manag. 16 (2020) 11.
[44] C. Stefanutti, U. Julius, G.F. Watts, M. Harada-Shiba, M. Cossu, V.J. Schettler, G. De Silvestro, H. Soran, J.R. Van Lennep, L. Pisciotta, H.U. Klör, Toward an international consensus—integrating lipoprotein apheresis and new lipid-lowering drugs, Journal of Clinical Lipidology 11 (4) (2017) 858–871.
[45] NHS Gloucestershire Hospitals, Lipoprotein (a). https://www.gloshospitals.nhs.uk/our-services/services-we-offer/pathology/tests-and-investigations/lipoprotein/, 2019.
[46] Lab Tests Online, Lp(a), Accessible at: http://www.labtestsonline.fr/tests/Lpa.html?tab=5, 2009.
[47] S.M. Marcovina, J.J. Albers, Lipoprotein (a) measurements for clinical application, JLR (J. Lipid Res.) 57 (4) (2016) 526–537.
[48] NICE, Familial hypercholesterolaemia: identification and management, Accessible at: https://www.nice.org.uk/guidance/cg71, 2019.
[49] NICE, Cardiovascular disease: risk assessment and reduction, including lipid modification, Accessible at: https://www.nice.org.uk/guidance/cg181, 2016.
[50] R. Klingel, A. Heibges, C. Fassbender, Lipoprotein (a) and mortality—a high risk relationship, Clinical Research in Cardiology Supplements 14 (1) (2019) 13–19.
[51] Novartis, Lp(a) Diagnostic Landscape Assessment – EU5 Presentation", 2020.
[52] LADR, Die familiäre hypercholesterinämie – genetische diagnostik, Accessible at: https://ladr.de/familiaere-hypercholesterinaemie, 2019.
[53] S. Tsimikas, S. Fazio, K.C. Ferdinand, H.N. Ginsberg, M.L. Koschinsky, S. M. Marcovina, P.M. Moriarty, D.J. Rader, A.T. Remaley, G. Reyes-Soffer, R. D. Santos, Unmet needs in understanding lipoprotein (a) pathophysiology: NHLBI working group recommendations to reduce risk of cardiovascular disease and Aortic Stenosis, J. Am. Coll. Cardiol. 71 (2) (2018) 177.
[54] S. Tsimikas, A test in context: lipoprotein (a) diagnosis, prognosis, controversies, and emerging therapies, J. Am. Coll. Cardiol. 69 (6) (2017) 692–711.