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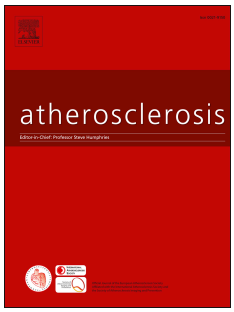

Is Lp(a) ready for prime time use in the clinic? A pros-and-cons debate

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Is Lp(a) ready for prime time use in the clinic? A pros-and-cons debate

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Abstract

Lipoprotein (a) (Lp(a)) is a cholesterol rich lipoprotein known since 1963. In spite of extensive research on Lp(a) there are still numerous gaps in our knowledge relating to its function, biosynthesis and catabolism. One reason for this might be that apo(a), the characteristic glycoprotein of Lp(a), is expressed only in primates. Results from experiments

using transgenic animals therefore may need verification in humans. Studies on Lp(a) are also handicapped by the great number of isoforms of apo(a) and the heterogeneity of apo(a)-containing fractions in plasma. Quantification of Lp(a) in the clinical laboratory for a long time has not been standardized. Starting from its discovery, reports accumulated that Lp(a) contributed to the risk of cardiovascular disease (CVD), myocardial infarction (MI) and stroke. Early reports were based on case control studies but in the last decades a great deal of prospective studies have been published that highlight the increased risk for CVD and MI in patients with elevated Lp(a). Final answers to the question of whether Lp(a) is ready for wider clinical use will come from intervention studies with novel selective Lp(a) lowering medications that are currently underway. This article expounds arguments for and against this proposition from currently available data.

1. PRO: Karam Kostner and Gert Kostner

1.1 History, structure and metabolism of Lp(a)

Lipoprotein (a) (Lp(a)) belongs to the class of cholesterol/ester rich lipoproteins spanning a wide range of plasma concentration ranging from <1 mg/dl to 300 mg/dl (approx. 2.5–750 nmol/L) and even more[1]. At the time of its detection by K.Berg in 1963 it was considered as a polymorphic form of LDL[2]. Yet it became apparent that Lp(a) is a complex of "normal" LDL with the specific glycoprotein apolipoprotein (a) (apo(a)) linked to apoB-100 by a disulfide bridge[3]. Cloning of apo(a) in 1987 revealed its striking homology to plasminogen[4]. A characteristic feature of apo(a) is its kringle structure where a homologous kringle-4 (K-4) of plasminogen is tandemly repeated between 11 and up to some 50 times together with one copy of K-5 and the (inactive) protease domain. This size polymorphism accounts for approx. 50% of the genetic variation of plasma Lp(a) levels[5]. Other variations in the apo(a) gene or in genes modulating Lp(a) metabolism add another 40% of the variability in plasma L(a) levels[6]. Of interest is the so-called "null-allele" causing the expression of a truncated form of apo(a) that is rapidly catabolized[6]. Thus, Lp(a) concentrations are approximately 90% genetically determined yet other modulators of its abundance exist in plasma.

Despite of intensive research many gaps exist in our knowledge related to Lp(a) biosynthesis and catabolism. As mentioned, Lp(a) is assembled from LDL and apo(a), yet there is a continuous dispute of whether this assembly occurs in the liver cell or outside in the plasma compartment[7]. An appealing suggestion is that once apo(a) is formed and secreted it attaches to the surface of parenchymal liver cells and bypassing apoB containing lipoproteins associate with apo(a) followed by the stabilization of their structure by a disulfide bridge. This may account for the observation that apo(a) distributes over the whole lipoprotein density range and its presence is not restricted to the "pre-ß lipoprotein" or the HDL-1 band.

Several research groups have shown that plasma Lp(a) levels stay relatively constant throughout life in healthy individuals and are barely influenced by diet or drugs[1]. An important question therefore was how apo(a) biosynthesis might be regulated. Patients with obstructive liver disease and high plasma levels of bile salts have extremely low Lp(a) concentrations after allowing for their genetic background, and this is reversed as soon as plasma bile salts normalize[8]. This led us to the elucidation of the transcriptional regulation of apo(a) expression through FXR signaling [9]. FXR activation has dual effects as it leads to the

dissociation of the transcription factors P-ELK-1 and HNF4α from the apo(a) promoter and down-regulation of transcription[1].

1.2 Pathophysiology and proposed mechanisms related to atherosclerosis

Apo(a) immuno-reactivity has been demonstrated in vascular atherosclerotic lesions and its abundance correlates with the plasma concentrations of Lp(a) [10-12]. Four pathophysiological mechanisms contribute to the relationship of Lp(a) to atherosclerosis and coronary artery disease[13-15]. This evidence is derived from *in vivo* studies in man, transgenic animals and *ex vivo* cell culture experiments.

1. Lp(a) binds with greater affinity to proteoglycans and extracellular matrix than LDL[16]. These aggregated Lp(a) complexes are avidly taken up by macrophages leading to foam cell formation which promote the formation of fatty streaks and atherosclerotic plaques.
2. Due to the kringle structure of apo(a) and its homology to plasminogen, apo(a) binds with high affinity to fibrinogen[17]. This prevents binding of plasminogen to fibrin clots and interferes with fibrinolysis and inhibits activation of plasmin formation by TPA[18].
3. Plasmin is responsible for the proteolytic activation of TGF-ß. Inhibition of plasmin formation by Lp(a) therefore blocks TGF-ß1 which acts as an autocrine inhibitor of human smooth muscle cell proliferation hence promoting vascular stenosis[19].
4. Lp(a) has a high affinity for oxidized phospholipids: Phospholipids are integral components of plasma lipoproteins and cell membranes. Under conditions of increased oxidative stress caused by inflammatory stimuli, reactive oxygen species are formed that lead to the oxidative modification of phospholipids (ox-Phos) and other unsaturated lipids. Ox-Phos have been found to bind specifically to Lp(a) and are immunologically highly active[20]. Ox-Phos activated Lp(a) interacts with lymphocytes and macrophages thereby aggravating further inflammatory processes. Of note, Lp(a) has been found to cause aortic valve calcification[21]. The molecular mechanism of this process appears to be related to ox-Phos modified Lp(a). Autotaxin (ATX) that is overexpressed in mineralized aortic valves is a lysophospholipase-C that hydrolyses ox-Phos into lysophosphatitic acid (LPA) [22]. LPA is a very bioactive compound that triggers many inflammatory processes including fibrosis.

All these well documented processes in atherogenesis triggered by Lp(a) provide compelling evidence that Lp(a) is causally related to atherogenesis, calcification, coronary artery and cardiovascular disease.

1.3 Epidemiological evidence

We believe that Lp(a) is the single most common genetically-inherited risk factor for early coronary heart disease and calcific aortic valve stenosis (CAVS)[14, 23]. There is little doubt in the scientific community that Lp(a) is strongly atherogenic and some experts consider Lp(a) to be the most important risk factor for CAD. This is substantiated by studies in animals and in man. First reports have been published by Berg who demonstrated that patients with CAD exhibited an extra pre-ß1 lipoprotein band on agarose gel electrophoresis[24]. Methods were devised to immunologically quantitate Lp(a) and these found that patients with MI exhibited significantly higher Lp(a) levels compared with controls[25]. Based on this relatively small case control study a cut-off concentration of 30 mg/dl as a "mild" risk factor and 50 mg/dl as a more significant one was suggested. Patients with combined high Lp(a) and high LDL-C levels were at significantly increased risk. Since that time, more that 2600 papers have been published and the majority have confirmed these results. It is impossible to review all of them here. Convincing evidence for the role of Lp(a) in CAD derives also from the prospective Munster Heart Study (PROCAM) study carried out in almost 5000 male participants aged between 40 and 65 years[26]. It concluded that "Lp(a) is a sensitive indicator of increased risk for major coronary events". Combining this data the meta-analysis of the Emerging Risk Factors Collaboration comprising >126.000 individuals calculated incidence rates for CAD comparing top and bottom tertiles for Lp(a) of 4.4 – 5.6[27].

Two important studies that support a causal role for Lp(a) as a CHD risk factor were published from Denmark. In the Copenhagen City Heart Study Lp(a) was shown to be a significant independent risk factor in both men and women over 10 years follow up of 9330 individuals [28]. Furthermore, in a prospective group of more than 40000 individuals in Denmark the risk of MI increased with Lp(a) concentrations[29]. Additional strong evidence of a causal relationship of Lp(a) with CVD comes from Mendelian randomization studies first published by Uterman *et al*.[30]. Importantly, elevated Lp(a) has been shown to be a cause for a special form of familial hypercholesterolemia[31]. Finally, evidence from several randomized, controlled LDL-C intervention trials with statins, niacin and proprotein convertase subtilisin

kexin-9 (PCSK-9) inhibitors have shown higher event rates in patients with elevated Lp(a) levels resulting in higher residual risk for CVD events.

1.4 Evidence for Lp(a) lowering

One of the difficulties with Lp(a) interventions is that most drugs that lower Lp(a) with the exception of selective anti-apo(a) antisense oligonucleotide (ASO) therapy, also affect other lipoproteins, such as LDL. This makes it very difficult to attribute clinically important effects to Lp(a) lowering. The strongest evidence that lowering Lp(a) reduces CVD risk comes from apheresis trials. A longitudinal multicenter cohort study with combined lipid apheresis and lipid lowering medication in patients with extremely high levels of Lp(a) showed a reduction in MACE of more than 80%[32]. A prospective observational multi-centre study from Germany also showed a significantly reduced incidence of CVD events in patients with elevated Lp(a) treated with apheresis[33] which was confirmed in the 5 year prospective follow up of the cohort[34]. In addition, nicotinic acid (niacin) reduces Lp(a) by up to 30 %[35] which was shown in the Coronary Drug Project in 1975 to reduce CVD events[36].

1.5 New therapies

Several novel drugs such as PCSK-9 inhibitors, mipomersen and lomitapide reduce Lp(a) but as they also affect LDL-C the extent of effect due to Lp(a) lowering is unclear. The PCSK-9 outcome studies are going to report their Lp (a) sub-study results soon and the results will shed some light on the clinical significance of Lp(a). The most direct Lp(a) therapy in clinical trials are antisense oligonucleotides targeting apolipoprotein(a). This therapy has not only shown to reduce plasma Lp(a) levels, but also oxidized phospholipids associated with Lp(a)[37]. Large clinical endpoint studies with this therapy will certainly add to our knowledge in this field.

1.6 Reliability of Lp(a) analysis in clinical laboratories.

Lipoprotein(a) has been quantified by all kinds of immunochemical methods. The most critical point with all methods without doubt is the selection of the reference material. Due to its size polymorphism Lp(a) exists in more than 30 isoforms with strikingly different particle size and molar mass[38]. Thus, Lp(a) is found in density gradient ultracentrifugation not only in the HDL_1 region between LDL and HDL_2 but may be found close to LDL or in HDL_2 (Fig.1). Moreover, apo(a) sticks to triglyceride rich lipoproteins (very low and intermediate density lipoproteins)[39] and last but not least Lp(a) forms complexes with LDL at

various ratios[40]. Finally, variable amounts of apo(a) fragments in plasma correlate with the Lp(a) concentration, are excreted into urine and correlate with the risk of CVD[41]. Irrespective of all these features, it is quite reassuring to note that commercial assays from different companies perform quite well in routine analyses. An important issue is that Lp(a) concentrations are expressed in different units. Molar units would be preferable, but this requires assays that are independent of apo(a) isoforms. Such assays are not readily available for high-throughput screening, yet most companies sell immuno-turbidimetric assays that are adequate for practical purposes. Conventionally Lp(a) concentrations are expressed in mass units and almost all large epidemiological studies use mass units yet there is currently a trend to switch to molar units, and conversion factors need to be applied. Some companies suggest a factor of 2.5, i.e. 1 mg/dl of Lp(a) corresponds to 2.5 nmol/L. Considering the composition of an Lp(a) particle, on theoretical grounds a conversion factor of 2.5 might be valid for an Lp(a) with the apo(a) isoform containing 25 K-4's. With 20 K-4's the factor would be 2.7 and so one. All these questions that are essentially academic in nature have been reviewed by consensus groups[14, 42]. These problems may be solved when apo(a) measurements are standardized by LC-MS[43]. The continuing work of the International Federation of Clinical Chemistry (IFCC)-Standardization Working Group of Apolipoproteins by Mass Spectrometry will likely solve the remaining problems[44](see also http://www.ifcc.org/ifcc-scientific-division/sd-working-groups/wg-apo-ms/).

Our confidence in the reliability of currently existing technologies are supported by two facts:

1. In 1981 we measured Lp(a) using an in-house assay and our own reference material in 76 male myocardial infarction (MI) patients and 107 controls. Based on the results of this study we proposed a conservative cut-off at 50 mg/dl and a more stringent one at 30 mg/dl for MI [25]. In subsequent very large trials using assays from various companies, these cut-off points were adopted [45]. Data from the EPIC-Norfolk Prospective Population Study, however, indicate that a cut-off of 50 mg/dl suggested by the EAS might be too high[46].2. More recently we assayed 160 plasma samples spanning an Lp(a) concentration of 1 mg/dl - > 150 mg/dl using 7 different commercial assays and found not only a very good correlation but also comparable mean and median values (H.Scharnagl *et al*. in preparation).

Considering these facts, we are convinced that for the time being the methodology available is sufficient for routine use.

1.7 Conclusions

In our opinion Lp(a) is ready for the clinic. Strong epidemiologic evidence that Lp(a) is the single most common genetically-inherited risk factor for early coronary heart disease and calcific aortic valve stenosis support its measurement in patients with premature CVD and premature stroke, in particular, but not exclusively in whom other risk factors fail to explain the presence of vascular disease. Lp(a) meets 9 of the original 10 criteria established by the World Health Organisation (WHO) for a biomarker to be used in screening programmes[47]. We also recommend Lp(a) measurement in FH patients as this group of patients frequently have higher Lp(a) concentrations in comparison to isoform-matched controls[48], and intermediate risk patients as assessed by classical CVD risk algorithms because patients can be re-classified into a higher risk category if Lp(a) is elevated above 50 mg/dl; this in turn should ultimately lead to more intensive management of treatable risk factors, especially LDL-C. By extension, we suggest measuring plasma Lp(a) levels in a wider population as outlined in Table.1 Whether Lp(a) lowering therapies are ready for clinical use will be determined by ongoing outcome trials, especially those which selectively target Lp(a) such as antisense therapy.

Table 1 here

CON: Anthony Wierzbicki

2.1 Function and Atherogenicity

Lipoprotein (a) is only found in humans, old world monkeys and hedgehogs[49]. The standard animal models of atherogenicity are mice and rabbits. Thus, all animal experimental data are, by definition, non-physiological. Physiologically Lp(a) consists of a number of particle subtypes ranging from very low density lipoprotein (VLDL) forms rich in apoE and triglyceride to a particle containing just apo(a) and $apoB_{100}$[5] (Figure 1). Though transgenic mouse models have been made they use human apo(a) and $apoB_{100}$ as mouse $apoB_{100}$ does not associate with human apo(a)[50]. Even monkey-based hepatocyte models are limited as they

lack Kringle (V) domains, lysine binding sites and may not contain oxidised phospholipid[51]. Whether these completely mimic human particle distributions and metabolism is unclear.

The mechanisms of assembly and especially clearance of Lp(a) are controversial. While some agreement exists about the post-translational and possibly intracellular assembly of Lp(a)[7] the mechanism of clearance remains obscure with pathways involving the VLDL receptor[52], apoE receptors, plasminogen receptor (PlgRKT)[53], and according to fashion the LDL (ApoE/ApoB$_{100}$) receptor being implicated[54]. Levels of Lp(a) expression in transgenic animal models are low at <20mg/dL in both mice and rabbits and limited to a single isoform[50]. Mice do not develop atherosclerosis without additional modifications such as knockout of apoE which impacts macrophage function, or to a lesser extent the LDL receptor. Few studies have been performed in LDL-receptor knockout mice and these make assumptions about the clearance of human-derived lipoproteins being similar to mouse analogues[50]. Thus, extrapolation from animal models makes many assumptions about Lp(a) particle handling that may not be true. Until recently, turnover studies of Lp(a) in humans have been difficult to perform despite abundance of literature for apolipoprotein B turnover and the presence of substantial Lp(a) concentrations in some individuals[55, 56]. One recent study shows divergent effects on Lp(a) fractional synthesis and clearance with PCSK-9 monotherapy compared with combination therapy with statins[57].

2.2 Methods and reliability of assessment

For reliable conclusions to be drawn from studies and for clinicians to have confidence in results ideally biochemical assays are standardised to reference materials so that patients attending clinics supported by different laboratories will receive consistent advice about the risk associated with any biomarker[58]. This is not the case for Lp(a) assays[59]. Many commercial kits based on enzyme linked immunosorbent assays (ELISA) or their

derivatives rely on polyclonal antisera, which include many that recognise Kringle (IV) domains and thus are subject to confounding by isotype[60]. Other methods using gradient ultracentrifugation[61, 62] or magnetic resonance techniques may give different results[63]. How these assays measure the different sub-fractions of Lp(a) (Figure 1) and especially the VLDL and apoE-rich fractions is unclear.

Figure 1 here

'Reference' values for total Lp(a) mass (mg/dL) are not based on standard reference materials. The approach used is a WHO/International Federation of Clinical Chemistry and Laboratory Medicine secondary reference material PRM-2B (21 x Kringle (IV) repeats; 107nM) whose characteristics can be expressed as nmol/L apo(a) and reflect particle numbers. A University of Washington monoclonal assay directed outside Kringle (IV) domains is used as a reference assay to allow inter-conversion for mass units in ELISA kit, but the commonly quoted factors of 2.0-2.5 are unreliable and not validated[42]. Consensus guidelines suggest the use of iso-type independent assays[64, 65] but these were not available or not used to derive much of the primary epidemiological data for the atherogenicity of Lp(a). Sample preservation is also an additional confounder as Lp(a) tends to aggregate unless preserved with trehalose[66] though samples with high Lp(a) may also show lower results after freeze-thaw cycles[42, 67]. Most error is likely to be in the direction of over-estimation of concentrations and hence CVD risk compared with baseline groups with negligible levels in Caucasian populations.

The main problem is that many laboratories use the Friedewald equation to calculate LDL-C concentrations. These determinations are known to provide an inaccurate underestimate in the presence of minimally elevated triglycerides[68, 69] but additional bias arises in patients treated with highly efficacious LDL-C lowering therapies – indeed clinical

trials often use ultracentrifugation to give valid results[70], and to deal with the over-estimation of LDL-C if the effects of high Lp(a) concentrations are ignored[71, 72]. The effects of correction for Lp(a) on diagnostic LDL-C criteria (>190mg/dL; 4.9mmol/l) and goals (<70mg/dl; 1.8mmol/L) have been investigated using 2 methods in 531,140 patients from the Very Large Database of Lipids (VLDL) study. Correction for Lp(a) reduced the proportion of patients with very high LDL-C from 1.4% to 0.86% (P<0.001) and established that those at LDL-C goal were not 16.7% but 23% (p<0.001). This discrepancy will have profound effects on the prescription of second or third line expensive drugs like PCSK-9 inhibitors whose initiation guidelines are related to LDL-C concentrations.

The problem with Lp(a) assays extend further. New lipid-lowering drug therapies are commonly tested for their effects on Lp(a) and many assume that the effects are consistent or unidirectional. A method comparison study of 7 methods assessing response to growth hormone (GH) therapy in patients with hypopituitarism showed that different Lp(a) assays showed divergent responses in patients initiated on GH treatment[73]. Translating the effects of Lp(a) from clinical trials using specialist assays to routine practice using less accurate methods is, therefore, difficult until standardisation is agreed.

2.3 Epidemiological evidence

The epidemiological evidence for Lp(a) is primarily based on Caucasian populations[27] with a high frequency of the 'null/minimal ' isotype pattern[29, 48, 74]. Yet Lp(a) distributions vary between human populations with high levels particularly found in West African-derived populations[75] and indeed this seems to be a gene in on-going evolution in man[49]. The amount of variance attributable to genetic factors is also lower in African populations at 65% compared to Caucasians where it is 95%[75]. Unfortunately, most epidemiological data is derived from European populations which essentially compare presence and absence of Lp(a)

given the high prevalence of low concentrations to derive CVD risk relationships. Numbers of affected patients with high concentrations of Lp(a) are small so confidence intervals increase yet strong positive associations are reported [27]. In European-African admixed populations (e.g. African-Americans) some data exist with studies such as Atherosclerosis Risk in Communities (ARIC) recording positive relationships in African-Americans[76] while others such as the Dallas Heart Study find a less strong relationship and ethnicity-specific modification by specific Lp(a)-related single nucleotide polymorphisms (SNPs) though an association of Lp(a) concentrations with CVD risk persists[77, 78].

There are few studies in native West African populations and even less in other African groups where Lp(a) concentrations are far higher than Caucasians and more normally distributed[79]. Indian, Hispanics (including American-Indian-derived populations) and Chinese tend to have intermediate Lp(a) distributions[80] and a more Caucasian profile of association with CVD risk but data is limited and variable between these groups[76, 77]. If a common risk limit cut-off for Lp(a) such as 75 nmol/L is used to define the risk for CVD, then 25% of Caucasian, 50% of West-African, and 10% of Japanese individuals would be considered at increased CVD risk[42]. Thus, much basic epidemiological work on Lp(a) as a worldwide CVD risk factor remains to be done as some associations from European populations do to seem to be replicated in West Africans[81].

The acid test for any biomarker is whether it reclassifies people at intermediate risk rather than just raising C-statistics (area under receiver operator characteristic curve). Data for Lp(a) is limited. In the Scottish Heart Health Extended (mostly Caucasian) cohort study of 15737 patients over 20 years Lp(a) did not add to the ASSIGN risk score in patients developing coronary heart disease (unlike high sensitivity troponin) but did in peripheral arterial disease[82]. Few studies have ascertained whether Lp(a) is superior in reclassification to questioning about a direct family history of coronary heart disease or CVD. In the Dallas

Heart study Lp(a) concentration only added to predictive power if associated with a family history of early onset coronary heart disease[78]. This suggests that only patients with high combined with null concentration Lp(a) allele isotypes are at significant risk but not those with combined intermediate levels as Lp(a) concentration is a co-dominant trait.

2.4 Evidence for intervention

Evidence for intervention on Lp(a) is minimal. Such evidence as exists it is derived from registries derived from small highly selected populations undergoing apheresis (n=1283)[34] including one small study (n=30) using a Lp(a) specific apheresis method and surrogate imaging outcomes[83]. The problem is that standard lipid lowering drugs such as statin, fibrates and ezetimibe have minimal effect on Lp(a) concentrations. Only niacin has been shown to reduce Lp(a) by 25-30%[35, 84, 85]. Niacin was shown in the original Coronary Drug Project in 1975 to reduce CVD events[36]. However, that drug has multiple effects on different lipid fractions. This dataset has never been analysed for Lp(a) and would likely be underpowered anyway due to its Caucasian population. Subsequent studies with niacin on background statin therapy have been disappointing in showing no clinical benefits and indeed some degree of harm[86]. A recent analysis of the Heart Protection Study-Treatment of HDL to Reduce the Incidence of Vascular Events (HPS2-THRIVE) trial by Lp(a) subgroups found no benefit despite an association of baseline Lp(a) with event rate and an average 12nmol/L reduction with niacin-laropiprant therapy extending to 34nmol/l in the top Lp(a) quartile[87]. The baseline data also suggested that raised Lp(a) concentrations would only account for 2% of CVD events in the whole population and only 6% in the top quartile suggesting that Lp(a) was a marginal risk factor for CVD[87]. Similar conclusions about the small role of Lp(a) are found in meta-analyses of epidemiological data[27].

Historical studies suggested that Lp(a) was a weak CVD risk factor and that adequate control of LDL-C negated its significance as a risk factor[88]. In the Familial Atherosclerosis Treatment study (FATS) of 146 patients, though Lp(a) was correlated with disease burden and in which niacin treatment, (which incidentally did not significantly change Lp(a) levels in FATS), was combined with statins and bile acid sequestrants only tight control of LDL-<2.5mmol/L (100mg/dl) was significant in determining progression of angiographic coronary disease[88]. A later analysis of LDL-C control from 2769 patients including 38% with Lp(a) concentrations >30mg/dL presenting for coronary angiography confirmed the relationship of Lp(a) with angiographic progression of disease (2.3 (1.7-3.2) fold risk) but again found that tight control of LDL-C to <1.8mmol/L (80mg/dl) negated the effects of elevated Lp(a) [89]. Furthermore, data from the study of dalcetrapib in acute coronary syndrome studies (Dal-Outcomes) showed that both in patients from the placebo (n=3170) and intervention groups (n=969) receiving aggressive anti-platelet therapy and adequately treated to control LDL-C as part of the initial optimisation protocol, Lp(a) was not a significant CVD risk factor in driving in-trial event rates[90]. Thus, if LDL-C is adequately controlled then Lp(a) is not a factor in driving progression of disease.

2.5 New therapies

Some of the novel therapies in development have effects in reducing Lp(a). Agents used in the treatment of homozygous familial hypercholesterolaemia such as mipomersen and lomitapide both reduce Lp(a) but no direct endpoint evidence is likely to be accrued with them simply due to small population sizes and problems with statistical power. Other more commonly investigated drugs such as PCSK-9 inhibitors reduce Lp(a) by 20-30% but data from intervention studies such as Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk (FOURIER) or ODYSSEY-Outcomes studies has not been published yet for Lp(a) subgroups.

2.6 Conclusions

Neophilia is a well-known disease of academe. Lipoprotein(a) is a well-characterised biomarker of unknown function associated with risk of CVD which has been the 'new' biomarker for CVD for the last 30 years. However, in practice, uncertainties about its measurement, population-specific reference values, and relationship to CVD events in well-managed populations mean that it cannot be used for any purpose except baseline CVD risk assessment[81, 91]. Even there it remains to be incorporated into standard risk measurement systems as some of the risk associated with Lp(a) may be captured by ethnicity or family history of cardiovascular disease. Thus, it fails the revised World Health Organisation criteria for a genetic biomarker to be used in screening[47]. It will also require studies with specific therapies capable of reducing Lp(a) substantially (e.g. 60-80%) in high-risk high Lp(a)-defined populations to prove whether intervention on Lp(a) is useful in the management of CVD.

Conflict of interest

The authors declared they do not have anything to disclose regarding conflict of interest with respect to this manuscript.

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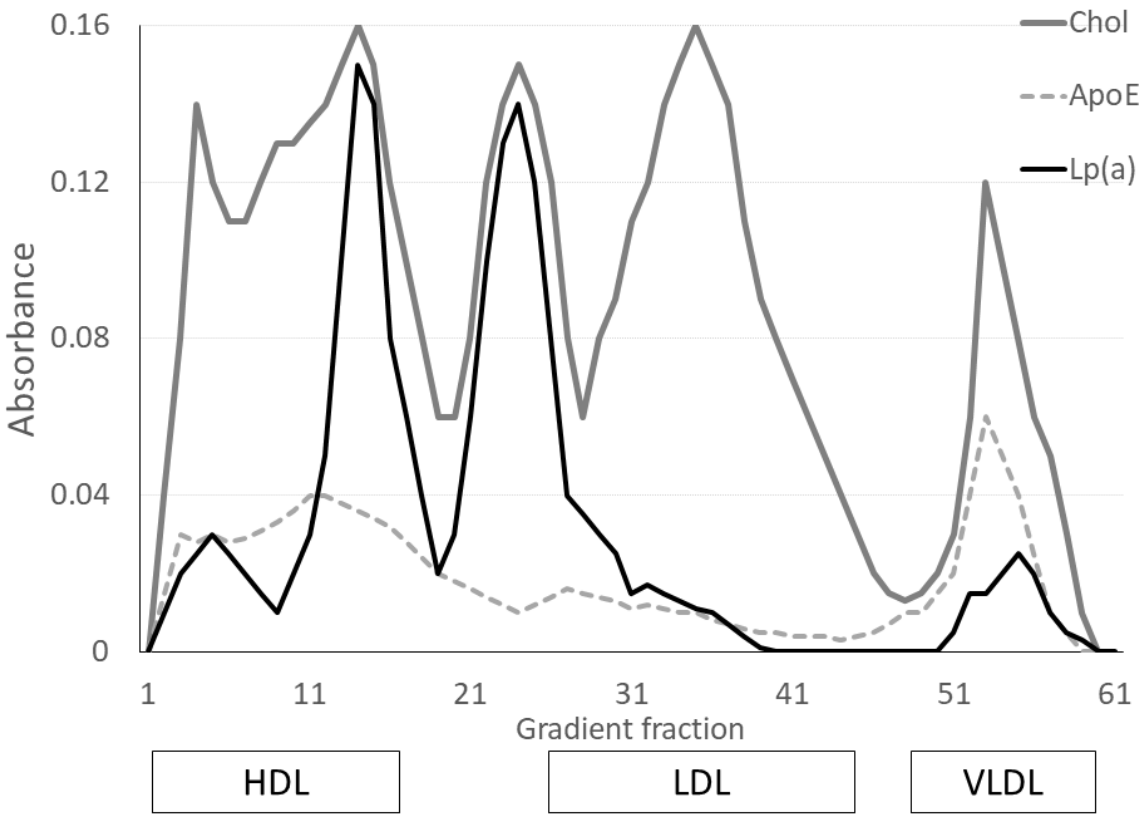
Figure 1

Gradient ultracentrifugation profile of an intensively statin-treated patient with baseline Lp(a) 3.56 g/L (Dako assay) showing profiles for cholesterol, apolipoprotein(a) and apolipoprotein E mathematically deconvoluted to identify different sub-fractions of Lp(a) with and without apoE.

Table.1 Recommendations for measurement of lp(a) under various conditions		
Group of individuals	**Characteristics**	**Comments**
Any healthy person with unknown Lp(a) and intermediate risk according to risk calculator	Populations on Western Type life style	In any lipid screening program Lp(a) should be measured once and incorporated into CV risk assessment
Familial hyper-Lp(a) and early CVD	If elevated Lp(a) is present in one of the parent, Lp(a) should be monitored in all family members	If Lp(a) values are << 30g/dl no further monitoring might be required
Patients with FH	In FH patients elevated Lp(a) appears to increase the risk of CVD	If Lp(a) levels are > 30 mg/dl more aggressive therapy may be warranted

- Currently recommended cut-off levels for Lp(a) are 30 or 50 mg/dl or 2.5 - 2.7 times higher using units in nmol/L. Drugs, hormones, inflammation and various diseases may cause significant changes in plasma levels that are partly reversible.



Is Lp(a) ready for prime time use in the clinic?

Highlights

- Lipoprotein (a) has been known to be a cardiovascular risk factor for many years but is not routinely measured
- Reasons to measure lipoprotein (a) based on epidemiology, assay methods and future interventions are presented.
- Reasons not to measure lipoprotein (a) based on assay methods, and current trial data are presented.