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REVIEW ARTICLE

Lipoprotein(a) and Cardiovascular Disease: Evidence, Recommendations and Emerging Therapies

Nathan D Wong[1]

Abstract

Lipoprotein(a) (Lp[a]) is a low-density lipoprotein (LDL) like particle which has atherogenic, proinflammatory and prothrombotic properties. Elevated in approximately 1 in 5 persons, increased levels of Lp(a) have been shown by epidemiological, genome wide association studies and Mendelian randomisation studies to be a causal factor for atherosclerotic cardiovascular disease (ASCVD). Lp(a) is primary genetically determined and is more atherogenic than LDL. Current recommendations from Europe, Canada, India and the United States recommend testing at least once in all adults. Persons found to have elevated levels (eg, > 50 mg/dL or > 125 nmol/L) are recommended for more intensive risk factor management, including further LDL-C lowering. With lipoprotein apheresis the only currently approved therapy for lowering Lp(a), several newer antisense oligonucleotide (ASO) and small interfering RNA (siRNA) therapies are in development and may soon provide additional therapeutic options for persons with elevated Lp(a). Several cardiovascular outcomes trials are underway involving these new therapies with the first to read out in 2026. Lp(a) is a key risk factor that warrants greater attention for testing, with further efforts to reduce ASCVD in those found to have elevated levels, especially in higher risk persons.

Key words: Cardiovascular diseases; Lipoproteins; LDL; Atherosclerosis.

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Introduction

Management of dyslipidaemia has long been established as a key target for cardiovascular disease (CVD) risk reduction. Current guidelines from Europe and beyond have focused on the control of low-density lipoprotein-cholesterol (LDL-C), with recommendations to achieve LDL-C levels < 55 mg/dL in highest risk patients with atherosclerotic CVD (ASCVD).[1] There is a wealth of evidence to support the LDL hypothesis, with statin trials consistently showing greater reductions of LDL-C to result in lower ASCVD event rates. More recently, clinical trials of proprotein convertase subtilisin kexin type 9 inhibitors (PCSK9i) show greater regression of atherosclerosis and lower ASCVD event rates down to LDL-C levels of at least 20 mg/dL with no evidence of a threshold effect.[2] However, despite statin therapy and well-controlled LDL-C levels, residual ASCVD risk is still present[3] due to inadequately controlled levels of other lipid and non-lipid factors. In this review we will discuss the importance of lipoprotein(a) [Lp(a)], including the evidence implicating it as a causal risk factor for ASCVD, its role in CVD risk assessment, recommendations on who should be tested, as well as existing and emerging therapeutic options for those with elevated Lp(a).

What is lipoprotein(a)?

Great attention in dyslipidaemia recently has emerged in our understanding of Lp(a), a critical risk factor for ASCVD and is composed of LDL-like particles with an apoB-100 covalently bound to an apo(a) by disulfide bonds (Figure 1). Lp(a) is primarily genetically determined and is proatherogenic, proinflammatory and prothrombotic. The apo(a) component contains 10 types of kringle IV (KIV) subtypes, along with an inactive protease-like domain and oxidised phospholipids. There are different Lp(a) isoforms, resulting from the number of KIV2 repeats which is highly variable and inversely related to the concentration of Lp(a).[4]

Lp(a) particles have been shown to be approximately 6-fold more atherogenic than LDL particles, motivating the significant attention to the former as a significant cause of ASCVD.[5] The Lp(a) gene is felt to have originally migrated out of Africa. Hence the prevalence of elevated Lp(a) > 100 nmol/L is highest in the African continent (approximately 30 %) (as well as in other populations of African descent), compared to about 25 % in South Asia and 20 % in North America and Europe.[6]

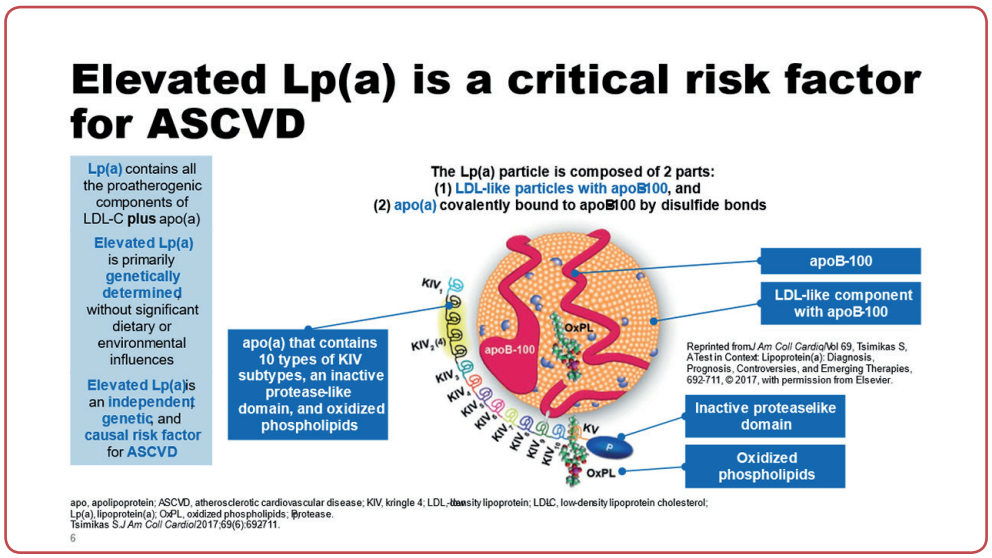


Figure 1: Elevated lipoprotein(a) is a critical risk factor for atherosclerotic cardiovascular disease (ASCVD)[4]

Evidence relating lipoprotein(a) to cardiovascular disease risk

A wealth of data from epidemiological, genome-wide association and Mendelian randomisation studies have shown the causal relation between elevated Lp(a) levels and CVD risk. Studies show a 3-4-fold increased risk of myocardial infarction, 3-fold increased risk of aortic valve stenosis, 1.6-fold increased risk of ischaemic stroke, 1.5-2-fold increased risk of heart failure, 1.3-fold increased risk of atrial fibrillation, 1.5-fold increased risk of CVD mortality and a 1.2-fold increased risk of all-cause mortality (Figure 2).[7-10]

More recent data from the Copenhagen General Population Study also shows those with the highest Lp(a) levels to have 2-3-fold increased risks of peripheral arterial disease, abdominal aortic aneurysm and major adverse limb events.[11] Others show elevated Lp(a), present in a third of patients with aortic stenosis, to be a strong predictor of progression of aortic stenosis.[12] Our recent pooling of 5 major US prospective studies comprising more than 27,000 adults without prior ASCVD with more than 20 years follow-up for future ASCVD events showed those in the highest quartile of Lp(a) averaging 53 mg/dL to have 46 % increased risks of ASCVD events, with a doubling of risks seen among those with baseline diabetes (Figure 3). Risks were strongest for the prediction of myocardial infarction and revascularisation. We

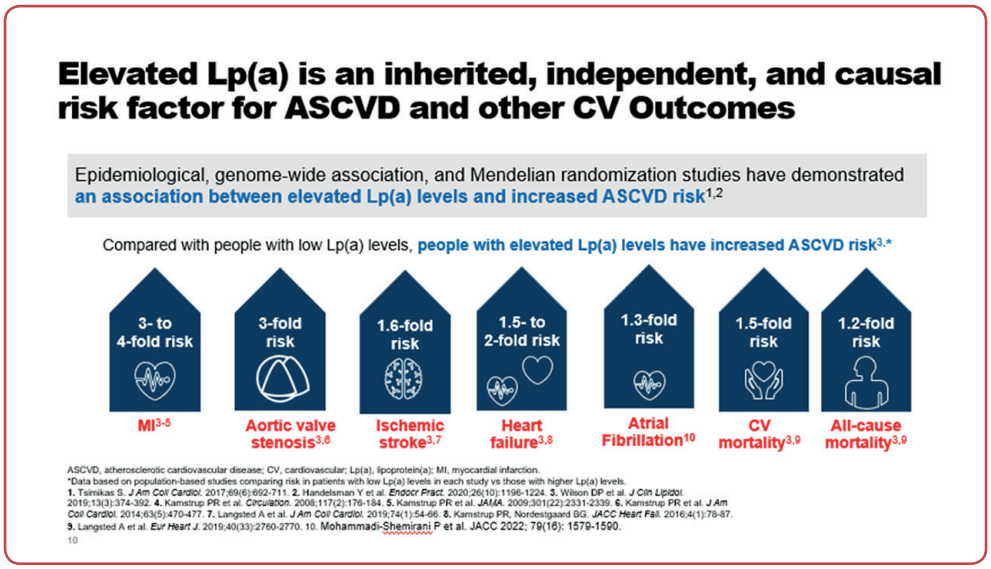


Figure 2: Elevated lipoprotein(a) as a causal risk factor for atherosclerotic cardiovascular disease (ASCVD) and other cardiovascular outcomes

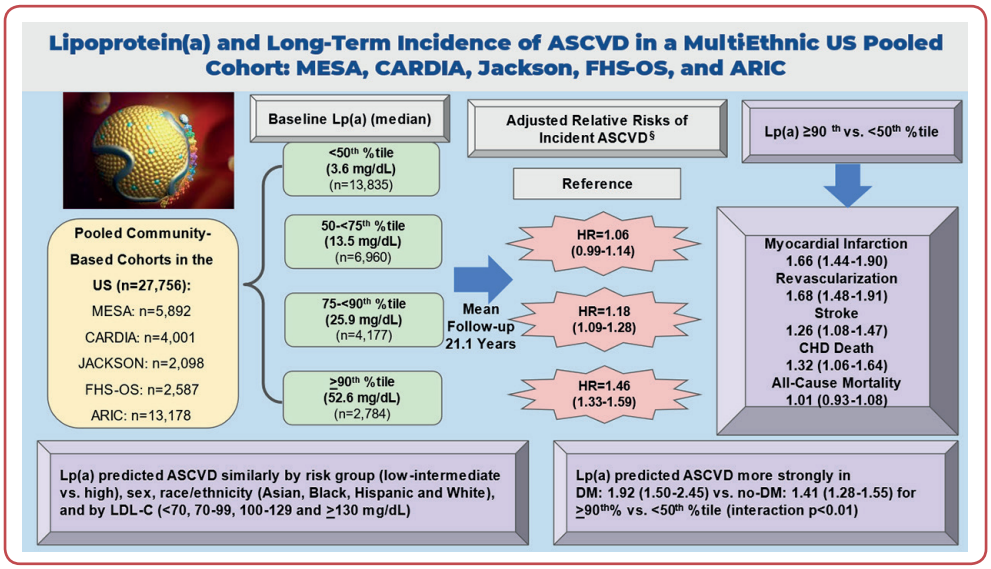


Figure 3: Lipoprotein(a) and long-term cardiovascular risk in a multi-ethnic pooled prospective cohort. From Wong et al[13]

also showed the consistency of Lp(a) for predicting ASCVD events comparing males and females and across major US race/ethnic groups.[13]

Moreover, in another recent study of patients from a large electronic health record registry among two hospitals in Boston, there was a plateauing of effect of Lp(a) in patients with prior ASCVD above levels above the 70th percentile (approximately 112 nmol/L) but a graded continuous increase which became significant above the 90th percentile (approximately 216 nmol/L) in those without prior ASCVD.[14] Bhatia and colleagues have also recently shown in a participant-level meta-analysis of over 27,000 participants from 6 placebo-controlled statin trials higher Lp(a) to be associated with ASCVD risk both in statin and placebo patients and among those on statins, an Lp(a) > 50 mg/dL (or > 125 nmol/L) was associated with increased risk regardless of achieved LDL-C level or absolute change in LDL-C.[15] Moreover, we have shown that Lp(a) to be the most important predictor of residual ASCVD risk in statin treated patients in the AIM-HIGH cohort with prior ASCVD and well-controlled LDL-C (Figure 4).[16]

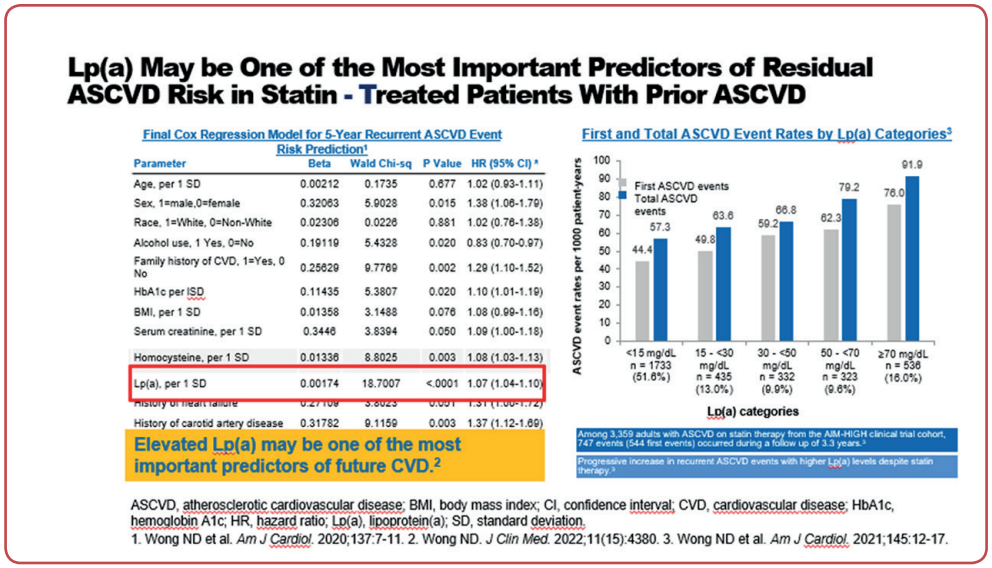


Figure 4: Lipoprotein(a) and residual atherosclerotic cardiovascular disease (ASCVD) risk in statin treated patients with prior ASCVD. From Wong et al[16]

Use of lipoprotein(a) in cardiovascular risk assessment

The foundation of preventive cardiology is CVD risk assessment to determine how aggressively patients should be treated. Risk scoring approaches including the European Score algorithm[17] as well as the US ASCVD Pooled Cohort Risk Score[18] incorporate only traditional risk factors. The added risk prediction Lp(a) provides warrants important consideration. The Bruneck population study showed that the addition of Lp(a) to traditional risk assessment enabled reclassification of about 40 % of intermediate risk persons, including 23 % of those not suffering a CVD event (non-cases) and 17 % of those experiencing a CVD event (cases).[19] The European Atherosclerosis Society recently recommended the incorporation of Lp(a) associated relative risk increases for different levels of Lp(a) to baseline 10-year ASCVD risk from the European Score algorithm.[20] A similar approach was also adopted by the American Heart Association, where a patients revised 10-year risk incorporating Lp(a) would be calculated as the baseline 10-year ASCVD risk x 1.11 (Lp(a) in nmol/L / 50) given the 1.11 hazard ratio observed from the UK biobank per 50 nmol/L (Figure 5).[21]

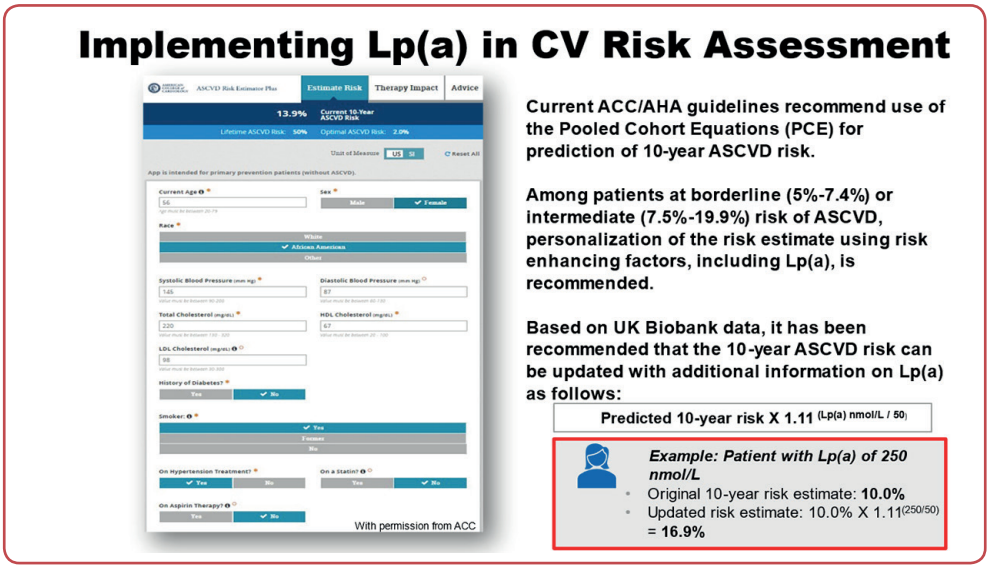


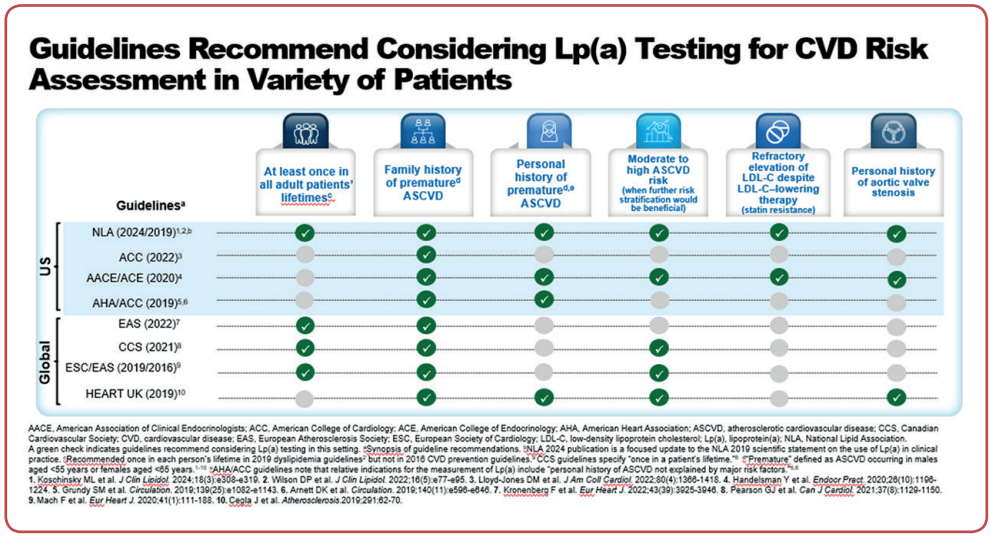
Figure 5: Implementing lipoprotein(a) in cardiovascular risk assessment

We have subsequently created a real-world Lp(a) risk score derived from an EHR cohort in the United States, validating it among 4 other population-based cohorts comprising approximately 20,000 adults. Our EHR model included Lp(a), age, sex, Black race/ethnicity, systolic blood pressure, total and high-density lipoprotein cholesterol, diabetes, smoking and hypertension medication. C-statistics for EHR and EHR+Lp(a) models in our EHR training data set were 0.7475 and 0.7556, respectively, with external validation in pooled cohort (n = 21 864) of 0.7350 and 0.7368, respectively. Among those at borderline/intermediate risk, the net reclassification improvement was 21.3 %.[22] It will be important for newer guidelines to consider incorporation of Lp(a) in risk scoring and CVD risk assessment in general.

Testing recommendations for lipoprotein(a)

Recent evaluations of medical claims data show 1 % of fewer of adults to be tested for Lp(a);[23,24] even among those with a personal or family history of ASCVD, testing rates are only 3-4 %.[24] Given the significant risks for ASCVD conferred by elevated Lp(a) levels, there is a great need to disseminate recommendations for more widespread Lp(a) testing. While higher risk persons, particularly those with a premature personal or family history of ASCVD or FH have long been recommended by several guidelines worldwide for Lp(a) testing, more recently European,[20] Canadian[25] and Lipid Association of India[26] recommendations have recommended universal screening in adults. The US National Lipid Association also recently revised its 2019 recommendations to recommend testing in all adults at least once (Figure 6).[27,28]

Importantly these recommendations also call for more systematic measurement in nmol/L units which are isoform independent, as opposed to mg/dL units which can be affected substantially by different Lp(a) isoforms resulting from varying numbers of KIV2 repeats as described above. There is now evidence that testing of Lp(a) and identifying those with elevated levels results in greater initiation of both statin (including high intensity statin) and non-statin therapy.[29] Health systems also need to make an effort to prompt physicians to test for Lp(a). At the University of California, Irvine, we recently implemented a best practice advisory (BPA) message sent to physicians with patients who have diagnosis of a personal or family history of ASCVD, familial hypercholesterolemia (FH), LDL-C ≥190 mg/dL, or aortic stenosis (Figure 7). This should also be reinforced by direct to patient messaging about the importance of seeing their physician for testing of Lp(a).



AACE, American Association of Clinical Endocrinologists; ACC, American College of Cardiology; ACE, American College of Endocrinology; AHA, American Heart Association; ASCVD, atherosclerotic cardiovascular disease; CCS, Canadian Cardiovascular Society; CVD, cardiovascular disease; EAS, European Atherosclerosis Society; ESC, European Society of Cardiology; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein(a); NLA, National Lipid Association.
A green check indicates guidelines recommend considering Lp(a) testing in this setting. [a]Synopsis of guideline recommendations. [b]NLA 2024 publication is a focused update to the NLA 2019 scientific statement on the use of Lp(a) in clinical practice. [c]Recommended once in each person's lifetime in 2019 dyslipidemia guidelines[2] but not in 2016 CVD prevention guidelines.[9] [d]CCS guidelines specify "once in a patient's lifetime."[8] [e]"Premature" defined as ASCVD occurring in males aged <55 years or females aged <65 years.[1,10] [f]AHA/ACC guidelines note that relative indications for the measurement of Lp(a) include "personal history of ASCVD not explained by major risk factors."[5,6]

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Figure 6: Clinical guidelines and consensus statements recommending lipoprotein(a) testing

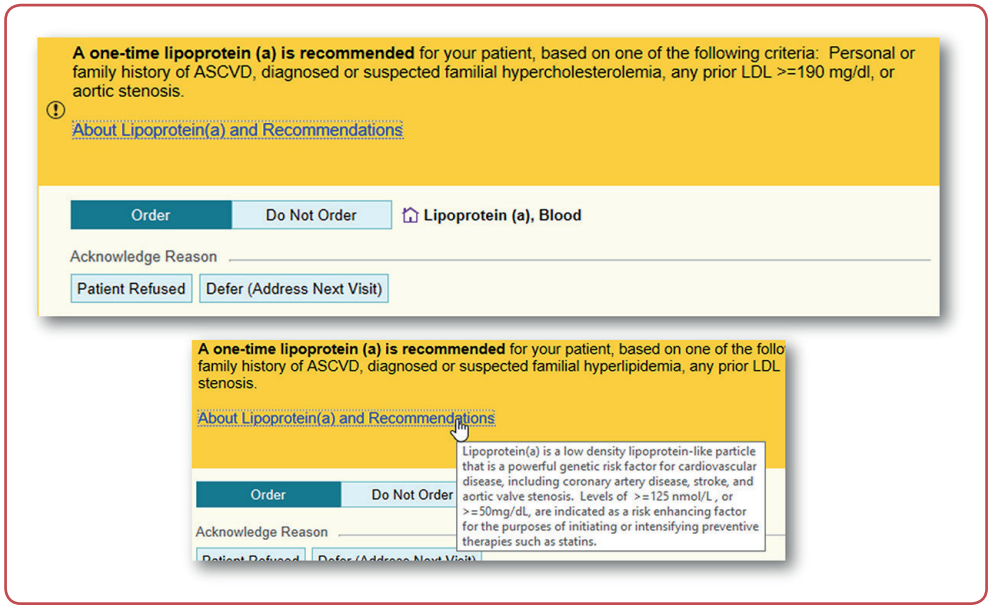

Figure 7: Lipoprotein(a) best practice advisory (BPA) at University of California, Irvine Health (implemented August 2023) (Wong ND)

Existing and emerging therapeutic options for lipoprotein(a)

Current recommendations call for more intensified treatment of all risk factors, including LDL-C in persons found to have elevated Lp(a), eg > 50 mg/dL or >125 nmol/L. While more intensified statin use and ezetimibe are normally the first opens to reduce LDL-C residual risk, they have a negligible effect on Lp(a) levels and some studies have shown statins can increase Lp(a).[20] PCSK9i therapies including alirocumab and evolocumab, as well as inclisiran, while not indicated to lower Lp(a), do result in approximately 25 % reductions in Lp(a); however, the clinical significance of such Lp(a) lowering from PCSK9i is not established. Lipoprotein apheresis currently remains the only approved therapy to lower Lp(a) and results in an acute reduction of Lp(a) levels by approximately 70 %; however, is labour intensive and quite expensive requiring infusions over several hours every 2 weeks in most cases, with availability limited at relatively few centres worldwide that provide the procedure.[20, 21, 28]

Motivating much of the excitement in the field is the ongoing development of antisense oligonucleotide (ASO), small interfering RNA (siRNA) and other therapies that directly target the production of apo(a) thereby inhibiting production of Lp(a). The ASO pelacarsen, which acts by forming a duplex with MRNA which is then recognised by the enzyme RNase H1 cleaves the mRNA preventing the formation of all types of protein including apo(a). Phase 3 data of pelacarsen shows average 80 % reductions in Lp(a) from once monthly subcutaneous injections.[29] The Horizon cardiovascular outcomes trial has enrolled over 8,000 patients with prior ASCVD and is the first and most widely anticipated trial involving pelacarsen of an Lp(a) agent and is expected to report out in 2026.[30] Olpasiran is a double-stranded siRNA therapy where the guide strand associates with a RISC complex, which causes apo(a) RNA to be degraded preventing the production of apo(a). Clinical trials of this therapy show up to complete inhibition of apo(a) production from every 3-month subcutaneous injections, resulting in up to 100 % reductions in Lp(a).[31] The Ocean(a) cardiovascular outcomes trial involving olpasiran is ongoing and expected to report out in the next few years.[32] A further siRNA therapy in development is zerlasiran, where phase 2 data shows approximate 80 % reductions in Lp(a) from injections every six months. A single dosage of another siRNA lepodisiran results in 97 % reductions in Lp(a) that appear to be largely sustained over a year.[33] A novel daily administered oral therapy in development, muvalapin, acts by disrupting the noncovalent ineraction of apo(a) and apo B, inhibiting the disulfide bond formation. Approximately 70 % reductions in Lp(a) based on an apo(a) assay

and > 80 % reductions based on an intact Lp(a) assay are observed from 60-240 mg/d dosages.[34] Obicetrapib is a new generation oral CETP inhibitor designed mainly for LDL-C lowering, but also shows 57 % reduction in Lp(a) levels, which may make it suitable for persons with both elevated LDL-C and moderately elevated Lp(a) levels.[35] Finally, but much earlier in development is a gene editing CRISPR-based approach acting at the DNA sequence level for permanent Lp(a) reduction from a single dosage.[36] It may be a number of years if and when the efficacy and safety of this novel approach for lowering Lp(a) can be demonstrated and the therapy made available.

Conclusion

Lp(a) is an under-recognised yet significant genetic causal factor for ASCVD. Elevations in Lp(a) are present in approximately 20 % of the population, higher in certain race/ethnic groups such as persons of African or South Asian descent. Its strong association with ASCVD event risk, particularly coronary artery disease, warrants greater education of its importance among both physicians and patients alike. Emerging therapies in development will hopefully soon provide for new therapeutic options for persons with elevated Lp(a) assuming positive results from ongoing cardiovascular outcomes studies.

Ethics

This study was a secondary analysis based on the currently existing data and did not directly involve with human participants or experimental animals. Therefore, the ethics approval was not required in this paper.

Acknowledgement

None.

Conflicts of interest

Dr Wong reports research support thorough his institution from Amgen and Novartis and is a consultant for Amgen, Novartis, Ionis and Heart Lung and a speaker for Novartis.

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Data access

The data that support the findings of this study are available from the corresponding author upon reasonable individual request.

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Author contributions

Conceptualisation: NW
Methodology: NW
Writing - original draft: NW
Writing - review and editing: NW
Visualisation: NW
Supervision: NW
Project administration: NW

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