Lipoprotein(a) and cardiovascular disease

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One in five people are at high risk for atherosclerotic cardiovascular disease and aortic valve stenosis due to high lipoprotein(a). Lipoprotein(a) concentrations are lowest in people from east Asia, Europe, and southeast Asia, intermediate in people from south Asia, the Middle East, and Latin America, and highest in people from Africa. Concentrations are more than 90% genetically determined and 17% higher in post-menopausal women than in men. Individuals at a higher cardiovascular risk should have lipoprotein(a) concentrations measured once in their lifetime to inform those with high concentrations to adhere to a healthy lifestyle and receive medication to lower other cardiovascular risk factors. With no approved drugs to lower lipoprotein(a) concentrations, it is promising that at least five drugs in development lower concentrations by 65–98%, with three currently being tested in large cardiovascular endpoint trials. This Review covers historical perspectives, physiology and pathophysiology, genetic evidence of causality, epidemiology, role in familial hypercholesterolaemia and diabetes, management, screening, diagnosis, measurement, prevention, and future lipoprotein(a)-lowering drugs.

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Introduction

High concentrations of lipoprotein(a) are a causal risk factor for cardiovascular disease,[1,2] similarly to high concentrations of LDL cholesterol.[3,4] Although high concentrations of lipoprotein(a) and LDL cholesterol both lead to atherosclerotic cardiovascular disease, high concentrations of lipoprotein(a) can also lead to aortic valve stenosis.[5,6] The evidence for causality for LDL cholesterol comes from both human genetics and randomised trials,[3] but has only come from human genetics for lipoprotein(a).[1,2,7–9] Concentrations of lipoprotein(a) are more than 90% genetically determined with minimal influence from lifestyle,[2] whereas LDL cholesterol concentrations are driven jointly by lifestyle and genetics.

Many pharmaceutical companies are at different stages of developing lipoprotein(a)-lowering medications. The drugs currently under development use either gene silencing of the *LPA* gene coding for apolipoprotein(a) to reduce plasma lipoprotein(a) concentrations by 80–98%,[10–13] or inhibition of lipoprotein(a) formation by blocking the binding of apolipoprotein(a) to apolipoprotein B to reduce plasma lipoprotein(a) concentrations by 65%.[14]

Renewed interest in high lipoprotein(a) has prompted worldwide guidelines and consensus statements on the prevention of cardiovascular disease to advocate for screening for high lipoprotein(a) concentrations, particularly in people at high cardiovascular risk[1,15–23] and in everybody once in their lifetime.[2,24–29] People at highest cardiovascular risk need to be identified to benefit from lipoprotein(a)-lowering therapy. Before such treatment becomes available, people identified as having a highest cardiovascular risk should be offered lifestyle changes and, if needed, pharmacological interventions to modify and manage other cardiovascular risk factors.

This Review focuses on the pathophysiology in the development of cardiovascular disease associated with high lipoprotein(a), screening for high lipoprotein(a), possible interventions in the absence of efficient lipoprotein(a)-lowering medication, and a description of the pipeline of new drugs. Other reviews detail other aspects of lipoprotein(a) and cardiovascular disease, including more comprehensive reference lists.[9,29–34]

What is lipoprotein(a)?

Lipoprotein(a) is a particle in plasma containing cholesterol, triglycerides, phospholipids, and apolipoprotein B, such as LDL and remnant lipoproteins.[31,35] It contains a unique apolipoprotein(a) that is covalently bound via a disulfide bridge to the apolipoprotein B component of the LDL particle (figure 1A). In evolution, the *LPA* gene coding for apolipoprotein(a) developed from the *PLG* gene coding for plasminogen.[46,47]

Apolipoprotein(a) and plasminogen share kringles IV and V and a protease domain.[2,30,31,35,46] Kringles, which are named after a Danish pastry due to their structure, are found in many proteins in the coagulation and fibrinolytic systems, and can bind to fibrin in blood clots.[48,49] Apolipoprotein(a) differs from plasminogen, first by having ten versions of kringle IV (subtype 1–10) versus only one in plasminogen, second by having a copy number variation in kringle IV subtype 2 ranging from one to more than 40 copies corresponding to different apolipoprotein(a) isoform sizes in plasma, and finally by having an inactive protease domain.[30,31,35] Plasminogen, unlike apolipoprotein(a), has kringles I, II, and III.

Search strategy and selection criteria

With a combined 47 years of experience in lipoprotein(a) research, we used accumulated knowledge and references from within this field. We searched PubMed and references from relevant articles for scientific evidence for this Review using the search terms "lipoprotein(a)" [MeSH] OR "lp(a)" AND "cardiovascular diseases" [MeSH] OR "acute-phase reaction" [MeSH] OR "Child" [MeSH]. We considered articles published in any language between Jan 1, 1963, and Feb 1, 2024, and selected the most relevant references.

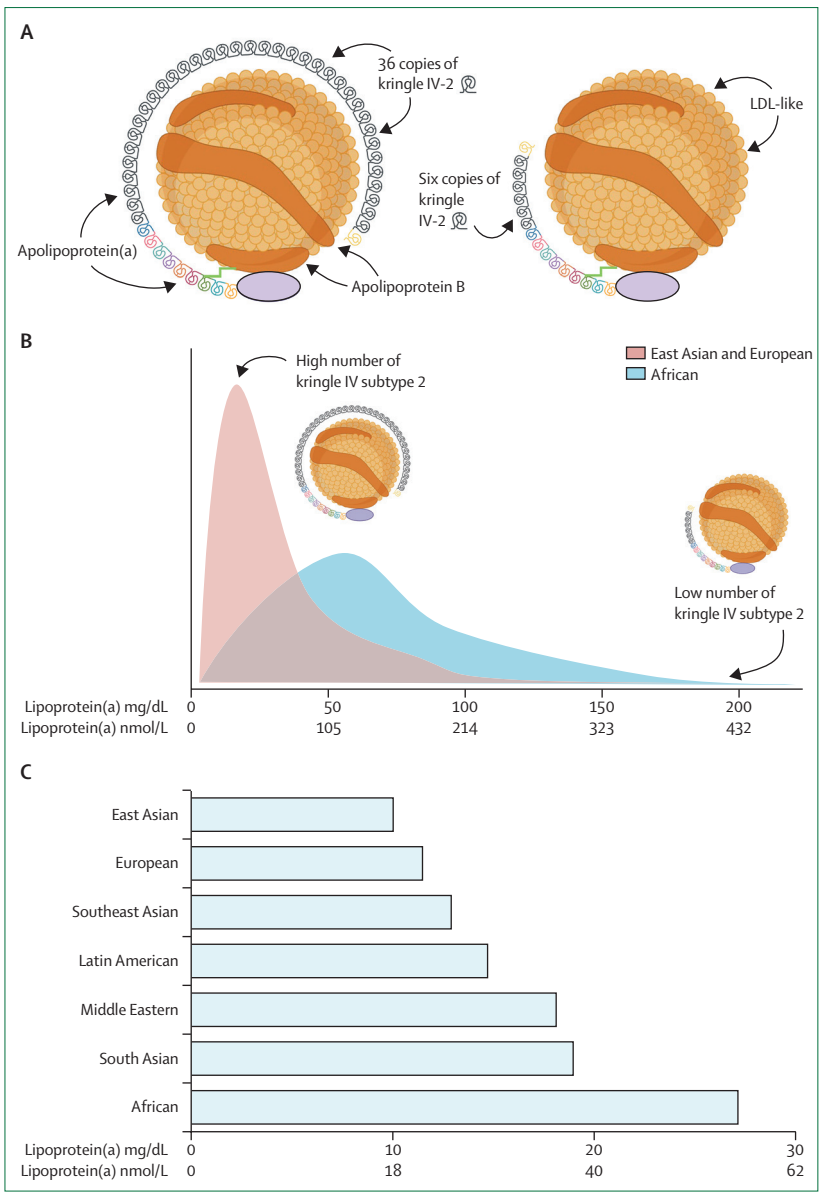

Figure 1: **Structure and plasma concentrations of lipoprotein(a)**
(A) The unique apolipoprotein(a) is attached to apolipoprotein B by a disulfide bridge at kringle IV subtype 9. This shows one version of the lipoprotein(a) particle with six repeats of kringle IV subtype 2, found mainly in individuals with high plasma lipoprotein(a) concentrations, and one version with 36 repeats of kringle IV subtype 2, found mainly in individuals with low plasma lipoprotein(a) concentrations. (B) Lipoprotein(a) concentrations in relation to number of kringle IV subtype 2 and (C) typical median plasma lipoprotein(a) concentrations in different ethnicities.[30,36–45] Figure partly created with BioRender.

Plasminogen that has converted to plasmin dissolves fibrin-containing blood clots (fibrinolysis), whereas apolipoprotein(a) will not promote fibrinolysis, as the protease domain is inactive.[31,46,48] Alternatively, in-vitro studies show that apolipoprotein(a) on lipoprotein(a) is capable of inhibiting blood clot lysis by inhibiting plasminogen conversion to plasmin and the positive feedback of more plasmin production, and increasing fibrinolysis in the presence of fibrin.[48]

Historical development

In 1963, the Norwegian physician Kåre Berg first described lipoprotein(a) in plasma.[50] However, scientific interest in this lipoprotein increased[32] only after Richard Lawn, Angelo Scanu, and colleagues described the *LPA* gene in 1987.[46] In the early 1990s, two prospective studies with little statistical power and poorly validated assays to measure lipoprotein(a) in frozen samples found that a high lipoprotein(a) concentration was not a predictor of high cardiovascular risk, which contrasted with findings from previous or parallel cross-sectional and case–control studies.[9,51,52] However, after the samples used for one of the prospective studies were retested with a well validated assay for plasma lipoprotein(a), high lipoprotein(a) was shown to be an excellent predictor of future cardiovascular disease.[53] Between 1998 and 2010, meta-analyses of prospective studies that associated high lipoprotein(a) with cardiovascular disease confirmed high lipoprotein(a) as a strong and robust risk factor for cardiovascular disease. These included studies on apolipoprotein(a) isoforms[54–57] and the two aforementioned negative studies.[51,52]

In 2009, renewed interest in high lipoprotein(a) came from two genetic studies that used kringle IV subtype 2 number of repeats and single nucleotide polymorphisms in the *LPA* locus; both studies observed that genetically high lipoprotein(a) is a causal risk factor for coronary heart disease.[7,8] These findings were later confirmed by similar or differently designed genetic studies.[2,32] Furthermore, in 2013, genetically high lipoprotein(a) was identified as a causal risk factor for aortic valve calcification and stenosis,[5] which was also later shown to be the case for high plasma lipoprotein(a).[6]

Based on this evidence, a 2010 European consensus recommendation suggested that individuals at high cardiovascular risk should have plasma lipoprotein(a) measured to evaluate additional cardiovascular disease risk, above risks conferred by other cardiovascular risk factors.[1] This advice is now found in lipid guidelines and consensus statements globally.[15–23] In 2019, European guidelines provided further recommendations, stating that everyone should have lipoprotein(a) measured once in their lifetime,[24] which was later endorsed by guidelines in India, Canada, China, and the USA.[25–29] In the same year, the first phase 3 lipoprotein(a)-lowering trial aimed at reducing cardiovascular disease began.

Physiology and pathophysiology

Although the physiological role of lipoprotein(a) is often considered unclear, genetic evidence shows that high concentrations of lipoprotein(a) are associated with morbidity and mortality, mainly after age 50 years (figure 2).

Apolipoprotein(a) developed independently twice in evolution (once in the hedgehog and once in Old World monkeys, apes, and humans),[30,35,63] suggesting that high lipoprotein(a) confers a survival advantage in young

mammals without access to modern medicine.[9,49] The homology between apolipoprotein(a) and plasminogen indicate a role in fibrinolysis, and the inhibition of fibrinolysis[48] leads to better wound healing, which could represent a survival advantage—eg, during childbirth.[9,49] Supporting this idea, lipoprotein(a) attaches to sites of arterial injury and fibrin accumulation (figure 3).[48,49,64]

After age 50 years, a similar pathophysiological mechanism in people with| high (>30 mg/dL [62 nmol/L]) concentrations of lipoprotein(a) could lead to the growth of thrombi through fibrinolysis inhibition at sites of atherosclerotic plaque rupture (figure 3), ultimately leading to increased risk of myocardial infarction and ischemic stroke.[9] At sites of minor arterial injury, including during turbulent flow, microthrombi might be incorporated into the arterial wall, leading to arterial stenosis and aortic valve stenosis.

Similarly to high LDL cholesterol, high lipoprotein(a) could theoretically also lead to cholesterol deposition in atherosclerotic plaques (figure 3). However, the cardiovascular disease risk increase from high lipoprotein(a) is substantially larger than that from the cholesterol and apolipoprotein B content of high lipoprotein(a),[58,65,66] supporting the idea that the mechanism by which lipoprotein(a) and LDL cholesterol lead to cardiovascular disease differ.

Population distribution by ethnicity and sex

Plasma lipoprotein(a) concentrations are lowest in people from east Asia, Europe, and southeast Asia, intermediate in people from Latin America, the Middle East, and south Asia, and highest in people from Africa (figures 1B and 1C).[30,36–45] In populations with the lowest concentrations, the population distributions are skewed with a tail towards high concentrations, whereas in populations with the highest concentrations, the population distribution approaches a normal distribution, although with a tail towards the highest concentrations (figure 1B). People from southeast Asia, Latin America, the Middle East, and south Asia also have distributions with a tail toward the highest concentrations.[38,39,63]

Concentrations of lipoprotein(a) are more than 90% genetically determined in all ethnicities, most importantly due to the number of repeats of kringle IV subtype 2 (figure 1B).[2] At high numbers of kringle IV subtype 2, many of the apolipoprotein(a) molecules are degraded within liver cells, whereas at low numbers of kringle IV subtype 2, the molecules are freely secreted to attach to LDL particles outside of liver cells to form lipoprotein(a).[67,68] Consequently, the number of kringle IV subtype 2 repeats is inversely associated with plasma lipoprotein(a) concentrations (figure 1B). In addition, many frequent and rare functional single nucleotide polymorphisms in and around the *LPA* locus modify the inverse correlation of number of kringle IV subtype 2 repeats and lipoprotein(a) concentrations.[2] Finally, lipoprotein(a) concentrations are 17% higher in women than in men after age 50 years, which typically coincides with the age of menopause.[37,69]

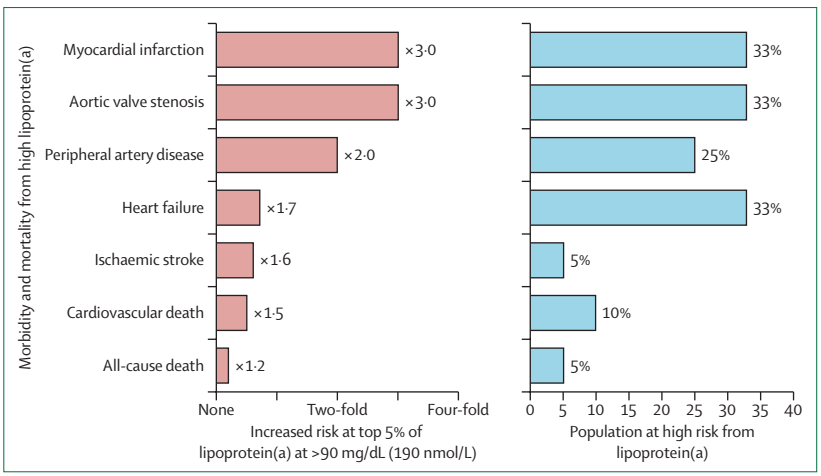

Figure 2: **Cardiovascular morbidity and mortality causally related to the highest plasma lipoprotein(a) concentrations**

Based on data from the Copenhagen City Heart Study and the Copenhagen General Population Study.[6,7,58–62] The risk of cardiovascular morbidity and mortality is for individuals within the top 5% of lipoprotein(a) concentrations, that is, more than 90 mg/dL (>190 nmol/L). For the percentage of the population at risk of cardiovascular morbidity and mortality for high versus low plasma lipoprotein(a), the higher risk is anywhere from 1·2 times the risk to the risk given for the top 5%.

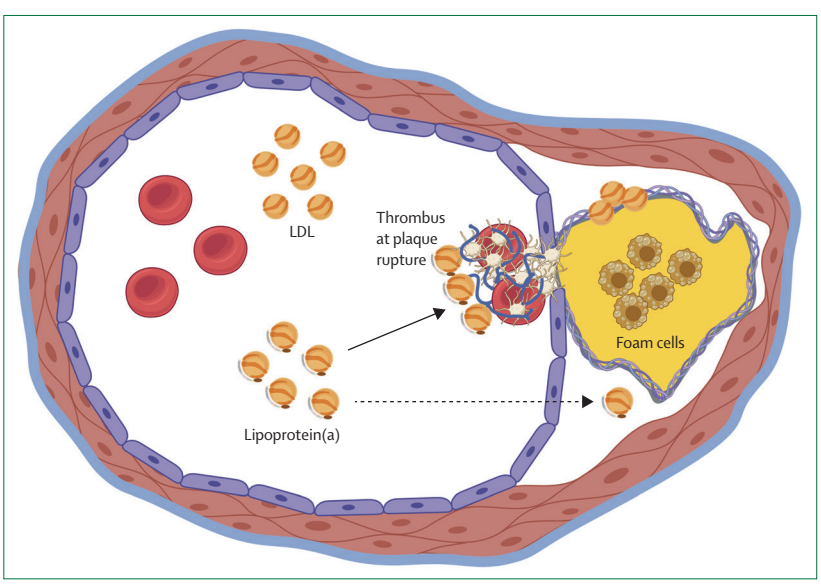

Figure 3: **Suggested role of high plasma lipoprotein(a) concentrations in thrombus growth at sites of atherosclerotic plaque rupture**

Lipoprotein(a) particles could, via kringle structures, attach to fibrin in the thrombus and inhibit plasmin-driven fibrinolysis, leading to thrombus growth and cardiovascular disease. Lipoprotein(a) could also deliver cholesterol for tissue repair and wound healing. Figure partly created with BioRender.

Measurement of lipoprotein(a)

As lipoprotein(a) concentrations remain similar throughout a person's life, concentrations should ideally be measured in the first lipid profile of any individual offered a test. For people with previously measured lipid

profiles, a lipoprotein(a) measurement should be included in the next lipid profile. Women who had a measurement before menopause should have an additional measurement about 5 years after age 50 years or menopause.[69] When therapy is available to lower lipoprotein(a), concentrations should be monitored to document the treatment effect.

All chemical pathology and clinical chemistry laboratories should offer lipoprotein(a) measurements on fresh samples, allowing timely reports of lipoprotein(a) concentrations with the standard lipid profile. Long-term freezing of samples can lead to falsely low concentrations.[32] Laboratories should use an assay largely independent of apolipoprotein(a) isoform size (equal to the number of kringle IV subtype 2 number of repeats; figure 1), which include an assay that uses five to six different calibrators with different apolipoprotein(a) isoform sizes.[32]

Theoretically, nmol/L is preferred for reporting lipoprotein(a) concentrations, whereas mg/dL works equally well for clinical purposes.[2] As of 2024, the Denka assay is commonly used in most lipoprotein(a) measurements worldwide. We used this assay to measure lipoprotein(a) concentrations in 14 000 individuals[58] with both units and observed a close relationship between them (coefficient of determination R^2=0·996): lipoprotein(a) in nmol/L=2·18×lipoprotein(a) in mg/dL−3·83. In this Review, we used this equation to show all lipoprotein(a) concentrations in both units. Laboratory reports should flag concentrations of more than 105 nmol/L or more than 50 mg/dL as abnormal to inform patients and clinicians about a high cardiovascular risk status.[18] This concentration cutoff represents slightly different percentiles for the general population of different ethnicities (figure 1C), but still indicates individuals at clinically important high risk of cardiovascular disease, irrespective of ethnicity or sex. As the risk of cardiovascular disease is similar at similar concentrations across different ethnicities,[2,37–39,42,63,70] the same cutoff in laboratory reports should be used for all ethnicities and all sexes.

In many countries, the greatest barrier to lipoprotein(a) awareness is the lack of universal funding of testing and expenses paid by the patient. The need to remove this barrier is urgent, particularly because the laboratory expense for measuring lipoprotein(a) is not higher than many other clinical biochemical tests. Another barrier is heterogeneity in lipoprotein(a) determination. Laboratories globally are using nmol/L (measuring particle number) rather than mg/dL (measuring total mass), and international standardisation will ensure that all assays accurately measure similar concentrations of lipoprotein(a).

When is lipoprotein(a) high?

Cardiovascular risk associated with higher lipoprotein(a) concentration is gradual and no formal cutoff exists.[2] However, for practical purposes, some thresholds can be mentioned. People with plasma lipoprotein(a) concentrations above 30 mg/dL (62 nmol/L) are at higher risk of cardiovascular disease compared with individuals with lower concentrations, although the risk increase between 30 mg/dL and 50 mg/dL (62–105 nmol/L) might be modest. The first consensus statement from the European Atherosclerosis Society on lipoprotein(a) agreed to identify lipoprotein(a) concentrations above 50 mg/dL (105 nmol/L) as being clinically important and indicative of a high risk of cardiovascular disease, suggesting that about one in five of the global population is at high cardiovascular risk.[1] Severe high risk of cardiovascular disease is often considered at lipoprotein(a) concentrations above 90 mg/dL (190 nmol/L), whereas concentrations of 130–391 mg/dL (280–849 nmol/L) correspond to the cardiovascular risk seen in individuals with familial hypercholesterolaemia (depending on the definition used to diagnose familial hypercholesterolaemia).[71]

Lipoprotein(a) as an acute phase reactant

After myocardial infarction there is a possible immediate decrease in lipoprotein(a) concentrations,[72] whereas concentrations thereafter can increase in relation to the patient's normal concentration by up to three times in the following 1–2 weeks.[73] These changes might be because lipoprotein(a) attaches to sites of injury to repair damaged tissue (figure 3).[9,49,64] Concentrations return to normal for the patient after around 1 month.[72,73] Lipoprotein(a), together with a standard lipid profile, should be measured immediately upon the admission of a patient with acute coronary syndrome or ischaemic stroke and again 1–3 months after the event. The initial measurement taken at admission secures an optimum diagnosis of lipid abnormalities in the patient, and the second measurement confirms that the initial value is correct and not influenced by the acute phase response immediately after the event. Although acute events, such as myocardial infarction, can influence lipoprotein(a) concentrations,[72,73] the opposite is not true, as high concentrations of lipoprotein(a) do not lead to low-grade inflammation.[74]

Cascade screening in families

Lipoprotein(a) measurement should also be offered to biological parents, siblings, and children of people with familial hypercholesterolaemia, or to individuals with a familial or personal history of high lipoprotein(a) or early atherosclerotic cardiovascular disease.[2,75] Systematic screening from index cases with both familial hypercholesterolaemia and high lipoprotein(a) identified one new case of elevated lipoprotein(a) for every 2·4 family members screened.[75]

Lipoprotein(a) as a cardiovascular risk factor

Genetic evidence of causality

Mendelian randomisation studies,[76,77] which are free of reverse causation and confounding, have been instrumental in documenting that a high lipoprotein(a)

concentration is causally related to cardiovascular disease.[1,2,9] This discovery has been possible as lipoprotein(a) concentrations are more than 90% genetically determined[2] and because variation within the *LPA* gene coding for kringle IV subtype 2 number of repeats is probably the genetic variant that explains the largest variation in a potential disease-causing factor in the entire genome.[77] In addition, many single nucleotide polymorphisms in and around the *LPA* locus can explain a large variation in plasma lipoprotein(a) concentrations, including for people with the same number of kringle IV subtype 2 number of repeats.[2]

This unique possibility led to the discovery that genetically high or low lipoprotein(a) concentrations are causally related to a high or low risk of myocardial infarction, respectively, and coronary heart disease, aortic valve stenosis, peripheral artery disease, heart failure, ischaemic stroke, and cardiovascular and all-cause mortality (figure 2).[1,2,5–9,58–62,78–80] Ongoing trials with medications will be needed to prove causality and investigate whether intensively reducing lipoprotein(a) lowers the risk of cardiovascular disease.

Clinical importance of high lipoprotein(a)

The relationship between high plasma concentrations of lipoprotein(a) and the extent of morbidity and mortality needs to be observed to understand the clinical meaning of genetic evidence of causality. On a relative risk scale based on studies from Copenhagen, Denmark, the highest risks were myocardial infarction and aortic valve stenosis, descending to peripheral artery disease and heart failure, and moving to the lowest risks of ischaemic stroke and cardiovascular and all-cause mortality (figure 2).[6,7,58–62] This ranking is similar across all sexes,[6,7,58–62] and is similar when based on data from the UK biobank.[78] For myocardial infarction, aortic valve stenosis, peripheral artery disease, and heart failure, with relative risks as high as 1·7 to three times for people with the top 5% of lipoprotein(a) concentrations, roughly a third of the global population are at high risk to some extent, whereas for ischaemic stroke and cardiovascular and all-cause mortality, with relative risks of 1·2–1·6 times, this risk is true for the top 5–10% (figure 2).[6,7,58–62] On an absolute scale of additional events per 10 000 person-years for high versus low lipoprotein(a) concentrations, myocardial infarction is most important, followed by aortic valve stenosis, heart failure, and ischaemic stroke.[2]

As lipoprotein(a) concentrations are more than 90% genetically determined, it can be argued that epidemiological observational studies with plasma lipoprotein(a) also represent Mendelian randomisation studies.[76,77] Typically, the risk of cardiovascular disease and other morbidity and mortality increases with high plasma lipoprotein (a) concentrations,[2,6,7,58–62] with the largest risk present in individuals with extremely high concentrations, as also illustrated in data from the UK Biobank.[2] This relationship is true for essentially all morbidity and mortality endpoints where causality has been documented (figure 2). In smaller studies, this relationship is difficult to show due to low statistical power. In the largest studies, such as those from Copenhagen (figure 2) and the UK Biobank,[2] high lipoprotein(a) concentrations lead to an increased risk of cardiovascular disease. Importantly, the risk of cardiovascular disease morbidity and mortality increases with high concentrations of lipoprotein(a) in all ethnicities and in all sexes.[2,37–39,42,63,70]

Although most evidence linking high lipoprotein(a) concentration to increased risk of cardiovascular disease is from individuals without baseline cardiovascular disease, high lipoprotein(a) is also associated with recurrent cardiovascular events.[2,70,81,82] The risk of cardiovascular disease from high lipoprotein(a) is independent of other cardiovascular risk factors, including concentrations of LDL cholesterol and C-reactive protein, and the presence or absence of statin therapy,[1,2,83,84] which is as expected for a largely, genetically determined trait according to the principle of Mendelian randomisation.[76,77]

Lipoprotein(a) in individuals with familial hypercholesterolaemia

Numerous early case-control and cross-sectional studies established that high lipoprotein(a) concentrations are more common in individuals with both heterozygous and homozygous familial hypercholesterolaemia than in people without, and that high lipoprotein(a) in familial hypercholesterolaemia increases the risk of coronary heart disease.[9]

As lipoprotein(a) contains cholesterol that is included in the measurement or calculation of LDL cholesterol, high lipoprotein(a), via its cholesterol content, contributes to the clinical diagnosis of familial hypercholesterolaemia in 25% of people who have been diagnosed.[85] Therefore, genetic variation in *LPA* coding for high lipoprotein(a) is arguably the second most common genetic cause of familial hypercholesterolaemia following genetic variants in the *LDLR* gene coding for the LDL-receptor.[85] Less common causes of familial hypercholesterolaemia are genetic variants in the *APOB* gene coding for apolipoprotein B and in the *PCSK9* gene coding for PCSK9.[86] However, not all experts agree that genetic variation in *LPA* is a direct cause of familial hypercholesterolaemia, as most regard high lipoprotein(a) as a separate additional risk enhancer in familial hypercholesterolaemia.

As 25% of people with familial hypercholesterolaemia with high lipoprotein(a) concentrations are at higher risk of coronary heart disease than the 75% of people without high lipoprotein(a),[71,85,87] diagnosed patients with high lipoprotein(a) require the most aggressive lowering of other cardiovascular risk factors.

Lipoprotein(a) and risk of diabetes

A notable finding among the extensive research on lipoprotein(a) over the years was that people with the

lowest concentrations of lipoprotein(a) have a slightly higher risk of type 2 diabetes than do those with higher concentrations.[88,89] A meta-analysis of eight studies found a consistent 38% higher risk of diabetes for people with the lowest lipoprotein(a) concentrations versus those with higher concentrations,[2] but genetic evidence for this association is conflicting.[2,89] Currently, the pathophysiology of the higher risk of diabetes with lower concentrations of lipoprotein(a) is not understood. The risk of an increase in diabetes diagnosis after substantial lipoprotein(a) lowering needs to be monitored in future trials of aggressive lipoprotein(a)-lowering therapy.

Lipoprotein(a) in children

Within the first 2 years of life, concentrations of lipoprotein(a) rise to those present during the rest of a person's life.[90] Lipoprotein(a) concentrations of more than 30 mg/dL (62 nmol/L) have been associated with a high risk of both first and recurrent ischaemic strokes in children and adolescents,[2] and therefore some centres seeing these young patients will screen for high lipoprotein(a).[29] However, a relationship between high lipoprotein(a) concentration and high risk of ischaemic stroke in children and adolescents should be interpreted cautiously, as underlying studies are small and occurrence of ischaemic stroke in children and adolescents is rare. In children and adolescents with familial hypercholesterolaemia and high LDL cholesterol, high lipoprotein(a) is associated with fast progression of carotid intima-media thickness.[91] As mentioned previously, lipoprotein(a) should be measured in anybody with, or suspected of having, familial hypercholesterolaemia, including children and adolescents.

Panel: Specific interventions in individuals with high lipoprotein(a) with the aim of reducing overall cardiovascular risk

Healthy lifestyle
- Stop smoking: no change
- Plant-based foods that are considered healthy: no change
- Avoid higher weight: no change
- Physical exercise: no change

LDL cholesterol reduction
- High-intensity statin: no change
- Ezetimibe: no change
- PCSK9 inhibitor: decrease by 25%
- Bempedoic acid: no change
- Apheresis: decrease by 35%
- Niacin: decrease by 25%

Blood pressure reduction
- Therapy advised in guidelines:[2,24,29,94] no change

Diabetes control
- Therapy advised in guidelines:[2,24,29,94] no change

Triglyceride and remnant cholesterol reduction
- Therapy advised in guidelines:[2,24,29,94] no change

Reduction in weight
- Therapy advised in guidelines:[2,24,29,94] no change

No change=no change in concentrations of lipoprotein(a)

Guidelines and screening

Cardiovascular prevention guidelines and consensus statements for European countries in general and specifically the UK, France, Poland, Canada, USA, India, and China advise to either measure plasma lipoprotein(a) concentration in people at highest cardiovascular risk or to measure lipoprotein(a) once in a lifetime in anyone potentially at cardiovascular risk.[1,2,15–29] The most common cardiovascular risk conditions mentioned in these guidelines and statements are a personal or family history of atherosclerotic cardiovascular disease, familial hypercholesterolaemia, moderate to high cardiovascular risk, family members with high lipoprotein(a), calcific aortic valve stenosis, and insufficient LDL cholesterol lowering despite aggressive therapy (statin resistance).[32]

For risk discrimination, in individuals with lipoprotein(a) concentrations of more than 50 mg/dL (105 nmol/L), 23% of individuals with a first myocardial infarction event reclassified correctly to a higher risk category, while no individuals with events were reclassified incorrectly to a lower risk category.[92] However, if the entire concentration range of lipoprotein(a) is considered, lipoprotein(a) only marginally improves risk discrimination.[2,92] Therefore, the reclassification of atherosclerotic cardiovascular disease risk should only be considered when lipoprotein(a) concentrations are high—eg, by taking into account both lipoprotein(a) and baseline absolute risk of atherosclerotic cardiovascular disease.[2] The combination of high lipoprotein(a) and high coronary calcium score can also identify people at an extremely high risk of atherosclerotic cardiovascular disease.[93]

Current management: prevention through risk factor control

Until efficient, safe, and approved lipoprotein(a)-lowering drugs become available, people with high lipoprotein(a) should be considered for the aggressive reduction of other known cardiovascular risk factors (panel).[2,24,29,94] Although most of these interventions have no influence on lipoprotein(a) concentrations, these interventions can reduce the patient's absolute risk of cardiovascular disease, thereby indirectly reducing the influence of the genetic cardiovascular risk from high lipoprotein(a).

Other than a healthy lifestyle,[24,95] aggressive LDL cholesterol reduction is crucial (panel), as high lipoprotein(a) has an influence on the risk of cardiovascular disease from pre-existing atherosclerosis, due to high LDL cholesterol and remnant cholesterol.[4,96]

Standard regimens to lower LDL cholesterol should be adhered to, such as an administered high-intensity statin followed by the addition of ezetimibe and PCSK9 inhibitors to achieve the LDL cholesterol goal needed.[24] For patients who are unable or do not consent to take a statin, bempedoic acid can be added to ezetimibe and PCSK9 inhibitors.

High-intensity statin therapy is the most important medication to be given to patients with high lipoprotein(a) and at high cardiovascular disease risk,[2] however, statins have no effect on lowering lipoprotein(a) (panel).[84] Although statins have been suggested to slightly increase lipoprotein(a) concentrations based on results from smaller studies,[33] individual-level data on participants in seven randomised, placebo-controlled, statin outcome trials found that statins had no effect on lipoprotein(a) concentrations.[84] Notably, even if statins increased lipoprotein(a) concentrations slightly, this effect would have minimal clinical impact compared with the well documented effect of statins in reducing cardiovascular disease and mortality.

PCSK9 inhibition reduces LDL cholesterol by 50–60% and lipoprotein(a) by 25% (panel), and patients with the highest lipoprotein(a) concentrations benefit substantially from PCSK9 inhibition.[97,98] In secondary prevention, novel evidence suggests that intensive LDL cholesterol reduction with monoclonal PCSK9 inhibitors can benefit patients with high lipoprotein(a) concentrations,[97,98] although evidence is not yet available for individuals with high lipoprotein(a) in primary prevention. In addition, lowering of lipoprotein(a) was associated with the cardiovascular benefit of PCSK9 inhibition.[97,98] However, as PCSK9 inhibition has never been tested selectively in patients with high lipoprotein(a) concentrations and high risk of cardiovascular disease, this drug class has no approved indication that lipoprotein(a) reduction can prevent cardiovascular disease.

In a few countries, but mainly in Germany, apheresis-lowering LDL cholesterol and lipoprotein(a) is offered every week or 2 weeks to patients with repeated cardiovascular events and lipoprotein(a) concentrations of more than 60 mg/dL (>127 nmol/L).[99,100] This therapy reduces lipoprotein(a) concentrations on average by 35%, with maximum reductions of 70% immediately after apheresis (panel). However, compared with pharmacological approaches for altering concentrations of lipoproteins, apheresis entails relative limitations in terms of availability in specialist apheresis centres, frequency of visits required for patients, and high yearly cost.[29]

Niacin reduces lipoprotein(a) by 25% (panel) and reduces LDL cholesterol, remnant cholesterol, and triglycerides. However, due to many side-effects and because niacin with statin therapy did not reduce cardiovascular disease events,[101,102] the use of niacin has declined or stopped in most countries.

Medical therapy for the reduction of blood pressure, triglycerides, remnant cholesterol, weight reduction for obesity, and diabetes control are important to consider in those with high lipoprotein(a). Reductions in other cardiovascular risk factors follow general guideline advise (panel).[24,94] No evidence or guidelines advise the use of aspirin for the prevention of atherosclerotic cardiovascular disease in the primary prevention setting for people with high lipoprotein(a); however, aspirin should be used in individuals already with atherosclerotic cardiovascular disease. As with other treatment modalities discussed in this section, no randomised trials have directly addressed the various treatments in individuals with high lipoprotein(a).

Future therapies

Over the past 10 years, many lipoprotein(a)-lowering drugs have been in various phases of development. Five of these drugs have reached the public domain through registered trials or publication of results from phase 1, 2, and 3 trials.[10–14] These drugs in development all aim to reduce the production of lipoprotein(a) through gene-silencing technologies or by inhibiting apolipoprotein(a) from binding to LDL particles.

The maximum lipoprotein(a) reductions that have been reported are 80% for pelacarsen, 98% for olpasiran, zerlasiran, and lepodisiran, and 65% for muvalaplin (figure 4).[10–14] Although pelacarsen, olpasiran, and lepodisiran are already being tested in phase 3 cardiovascular disease endpoint trials, zerlasiran and muvalaplin have not yet reached that stage (figure 4).

Pelacarsen[10] inhibits mRNA production from the *LPA* gene coding for apolipoprotein(a) in the nucleus of hepatocytes using an antisense oligonucleotide, and is administered by a once-monthly subcutaneous injection (figure 4). Olpasiran,[11] zerlasiran,[12] and lepodisiran[13] inhibit mRNA production from *LPA* within the cytosol

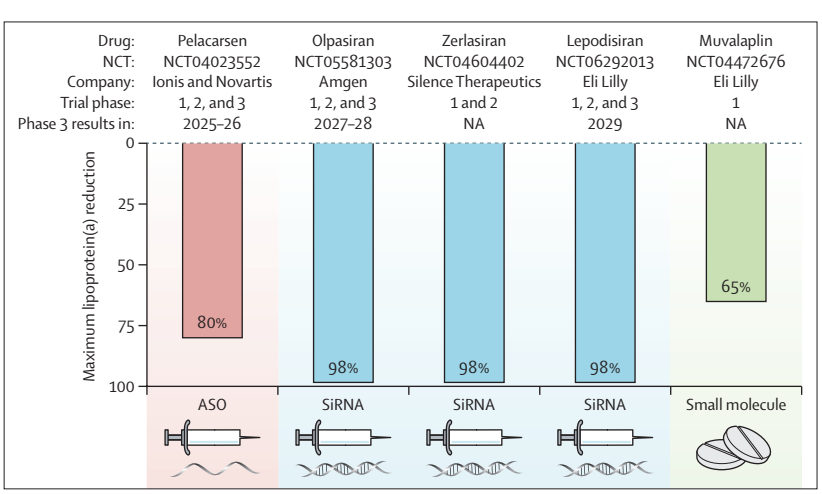

Figure 4: **Maximum achieved lipoprotein(a) reduction for five drugs in development**
ASO=antisense oligonucleotide. NA=not applicable. SiRNA=small interfering RNA.

of hepatocytes and are injected subcutaneously two to four times yearly. Muvalaplin[14] inhibits the attachment of apolipoprotein(a) covalently to apolipoprotein B on LDL particles outside hepatocytes, and needs to be taken orally every day.

The randomised, double-blind, Lp(a)HORIZON trial (NCT04023552) of pelacarsen has enrolled 8323 patients with established atherosclerotic cardiovascular disease and lipoprotein(a) concentrations that are 70 mg/dL or more (≥145 nmol/L). The primary composite endpoint is cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, and urgent coronary revascularisation.

The randomised, double-blind, OCEAN(a) trial (NCT05581303) of olpasiran has enrolled 7297 patients with established atherosclerotic cardiovascular disease and lipoprotein(a) concentrations that are 200 nmol/L or more (≥94 mg/dL). The primary endpoint is cardiovascular death, non-fatal myocardial infarction, and urgent coronary revascularisation.

The randomised, double-blind, ACCLAIM-Lp(a) trial (NCT06292013) of lepodisiran plans to enrol 12 500 patients with established atherosclerotic cardiovascular disease or who are at high risk of cardiovascular events, together with lipoprotein(a) concentrations of 175 nmol/L or more (≥82 mg/dL). The primary endpoint is coronary heart disease death, non-fatal myocardial infarction, stroke, and urgent coronary revascularisation.

Other drugs are also being investigated for their effects on lowering high lipoprotein(a) concentrations, such as oral PCSK9 inhibitors, cholesterol ester transfer protein inhibitors, and gene editing, which are all in clinical trials at this stage. However, none of these other novel drugs are yet testing whether lowering high concentrations of lipoprotein(a) will reduce the risk of cardiovascular disease.

Conclusion

High concentrations of lipoprotein(a) are a causal risk factor for cardiovascular disease in 20% of the global population, and novel therapies are in development with the potential to reduce the risk of high lipoprotein(a). It is therefore timely to measure plasma lipoprotein(a) in all people at risk of cardiovascular disease once in a lifetime, to offer those people maximum cardiovascular risk factor control, and to identify individuals who will likely benefit from lipoprotein(a)-lowering therapy.

Contributors

BGN and AL were responsible for the conception of the content of the Review, including the figures. BGN wrote the first draft of the manuscript. Both authors contributed to the generation of the figures, had access to the study data used for the figures, directly accessed and verified the underlying data reported, contributed to the interpretation of data, revised the manuscript, and gave approval for publication.

Declaration of interests

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