



Progressive atherosclerotic cardiovascular disease associated with high lipoprotein(a) – the German experience with lipoprotein apheresis and future perspectives with lipoprotein(a) lowering drugs

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Abstract

Lipoprotein(a) (Lp(a)) exhibits proinflammatory and proatherogenic properties. Evidence from prospective epidemiological studies, as well as Mendelian randomization studies, reveals an independent and causal association between elevated Lp(a) concentrations and atherosclerotic cardiovascular disease (ASCVD). Lipoprotein apheresis (LA) effectively lowers atherogenic lipoproteins when medication is insufficient. Since 2008, LA reimbursement for patients with high Lp(a) (> 60 mg/dL) and progressive ASCVD has been approved in Germany. To justify this policy, German authorities required prospective data, leading to the conduct of the Pro(a)LiFe study and establishment of the German Lipoprotein Apheresis Registry (GLAR). The Pro(a)LiFe study enrolled 170 patients with high Lp(a) and progressive ASCVD to evaluate LA's long-term effect on cardiovascular event rates. Patients were investigated for 5 years before initiation of regular LA, then up to 12 years afterwards. Results showed a significant decline in mean annual cardiovascular events per patient from 0.27 (±0.25) in the 5 years before LA to 0.06 (±0.08) over the following 12 years ($p < 0.001$). Compared to a matched UK Biobank cohort, ASCVD event rates were higher before LA began and significantly lower afterwards. The results confirm that long-term treatment with LA is associated with low incidence of cardiovascular events in patients with high Lp(a) sustained over 12 years. Combining Lp(a) testing with LA has meaningfully reduced ASCVD events. Until Lp(a)-specific drugs receive regulatory approval, LA remains a viable treatment for selected high-risk patients. It will be important to assess whether results with novel pharmaceutical agents apply to the peculiar high-risk patients with high Lp(a) and progressive ASCVD.

Keywords: Lipoprotein apheresis, lipoprotein(a), atherosclerotic cardiovascular disease, therapy, prevention, reimbursement

1. Introduction

Lipoprotein(a) (Lp(a)) is a low-density lipoprotein containing apolipoprotein(a), with pro-inflammatory and pro-atherogenic properties. Evidence from prospective epidemiologic studies, as well as Mendelian randomization studies, reveals that elevated Lp(a) concentrations have an independent and causal association with atherosclerotic cardiovascular disease (ASCVD), including coronary artery disease (CAD), ischemic stroke (IS), peripheral arterial disease (PAD), and cardiovascular as well as all-cause mortality^[1-4]. Furthermore, recent studies have indicated an association between high Lp(a) concentration and the increased risk of developing calcific aortic valve stenosis^[5]. Median Lp(a) concentrations in European populations are around 10-11 mg/dL (22-24 nmol/L), but individual concentrations can range from < 0.1 to > 300 mg/dL (< 0.2 to > 645 nmol/L) mainly due to genetic variability observed at the *LPA* locus. A variable number of kringle-IV (KIV) type 2 repeats, causing a copy number variation in the *LPA* gene, is the basis for a protein size polymorphism with more than 40 isoforms^[6].

It is important to note for the considerations of this manuscript that conversion of Lp(a) concentrations from the mass unit mg/dL to the molar unit nmol/L is not exactly possible due to the isoform size polymorphism with variable molecular weights. It is not



standard practice to report mass and molar concentrations based on parallel measurements using tests calibrated for mass and moles. As a pragmatic approach for this manuscript, a factor of 2.15 was utilized to convert mass into molar values as recommended by Welsh *et al.*^[7], to show Lp(a) concentrations in both units. This factor gives very similar results as the equation suggested by Nordestgaard *et al.*^[3]: Lp(a) in nmol/L = $2.18 \times \text{Lp(a) in mg/dL} - 3.83$.

Lipoprotein apheresis (LA) is an effective option for lowering plasma concentrations of atherogenic lipoproteins in patients with severe hypercholesterolemia including familial hypercholesterolemia (FH). There are several methods of LA using different physicochemical principles like filtration, precipitation, or adsorption, to reduce atherogenic lipoproteins in particular low-density lipoprotein (LDL) particles including Lp(a) by > 60% to > 70% during a single extracorporeal treatment session^[8,9]. In addition, LA reduces plasma concentrations of proinflammatory and prothrombotic factors including fibrinogen, reduces blood viscosity, increases microvascular myocardial perfusion, and may provide beneficial effects on endothelial function^[8]. At present, LA stands as the sole targeted treatment option available for the reduction of Lp(a)-associated ASCVD risk.

This review article delineates the evolution of LA in Germany since 2008, when authorities determined that high Lp(a) with progressive ASCVD should be designated as an indication for chronic LA. The specific selection process, guided by the German reimbursement guidelines, is peculiar in that it identifies a select subgroup of patients with high Lp(a) levels and progressive disease despite the optimized treatment for other modifiable ASCVD risk factors. A substantial body of evidence has accumulated from these long-term experiences. Novel drugs offer promising perspectives that could expand the available therapeutic options. In the following discussion, we will address the potential of RNA and oral drug therapies to selectively lower Lp(a), as well as their implications for future LA utilization.

2. Reimbursement of Lipoprotein Apheresis in Germany

Since 1991, reimbursement of LA has been established in the guidelines of the statutory health insurance funds in Germany. Initial indications for chronic treatment included primary prevention in homozygous FH and secondary prevention in heterozygous FH or severe hypercholesterolemia, especially cases involving intolerance to lipid-lowering medications or progressive clinical courses. LA methods' ability to lower Lp(a) as effectively as LDL cholesterol (LDL-C) led to encouraging pilot experiences with a small number of patients with Lp(a)-hyperlipoproteinemia (Lp(a)-HLP) and strikingly progressive ASCVD, including coronary, peripheral, and cerebrovascular territories. A longitudinal cohort study including 120 patients characterized this subgroup of ASCVD patients for the first time before the reimbursement decision regarding Lp(a)-HLP^[10]. The mean annual major adverse coronary events (MACE) rate per patient was 1.06 before versus 0.14 during LA treatment. This difference was impressive, although the study has several weaknesses regarding selection of patients, and highly variable individual observation periods. Following intensive discussions between authorities and medical societies, in 2008 the German Federal Joint Committee (G-BA) decided to add Lp(a)-HLP > 60 mg/dL with progressive ASCVD evidenced clinically and by imaging techniques as an indication for chronic LA with regular reimbursement^[11,12]. With the new reimbursement decision, the G-BA stipulated that additional prospective data are required to prove the efficacy of LA for this indication and justify the decision's maintenance. Ethical concerns were raised about withholding LA from particularly high-risk patients assigned to the control group of a randomized trial who otherwise would have to be recommended a reimbursed treatment option. Due to this dilemma, the proposed protocol of a randomized controlled trial failed to achieve ethical approval.

Applications for LA treatment are compiled by apheresis centers. The eligibility for LA treatment is reviewed by regional committees of the Associations of Statutory Health Insurance Physicians case by case with final approval for reimbursement of patients' health insurance^[12,13]. The Lp(a) concentration must exceed 60 mg/dL, or the equivalent concentration of 120 nmol/L^[12,13]. Molecular analysis of Lp(a) isoforms in the Pro(a)LiFe study (Prospective Documentation of Isolated Lipoprotein(a)-Elevation with Progressive Cardiovascular Disease and Lipoprotein Apheresis for Effective Treatment of Hyperlipoproteinemia) patients offered the opportunity to validate and confirm the equivalence of 60 mg/dL and 120 nmol/L as Lp(a) thresholds in the context of the German LA reimbursement guideline by calculation of isoform specific concentrations^[13-15]. The LDL-C concentration should be within the normal range. This refers to a level that is close to the contemporary treatment targets when using the maximum tolerated dose of lipid-lowering medication. Since 2008, European Society of Cardiology (ESC)/European Atherosclerosis Society (EAS) targets for LDL-C in very high-risk patients have declined from 100 mg/dL (2.6 mmol/L), which was valid in 2008, to 70 mg/dL (1.8 mmol/L) since 2011 and 55 mg/dL (1.4 mmol/L) since 2019^[16]. ASCVD should be considered progressive if it persists despite the optimal treatment of all other modifiable cardiovascular risk factors. To conclude that Lp(a) was the decisive risk factor for the individual clinical course of ASCVD progression, applications must document progression by clinical and imaging techniques after LDL-C was close to target for a relevant duration. A positive family history of premature ASCVD is an important contributing factor in this context. Elevated Lp(a) and family history of premature coronary heart disease have an independent and additive association with long-term ASCVD risk^[17]. Approval does not include a specific number of ASCVD events.

The specific selection process guided by the German reimbursement guidelines is peculiar in that it identifies a select, currently non-quantifiable subgroup of patients with high Lp(a) levels and progressive disease, including recurring events despite the optimization of treatment for modifiable ASCVD risk factors. The 2025 update to the 2019 ESC/EAS guidelines acknowledged the

existence of these patients by introducing the category of extreme cardiovascular risk, which includes recurrent events^[17]. Regarding German experiences since 2008, it should be noted that aortic valve pathologies developing before commencing regular LA, although being a general characteristic of Lp(a) associated risk, did not play a relevant role in the indication of lipoprotein apheresis. Since its implementation in 2008, the German LA guideline has proven effective in identifying a very high-risk group of patients for treatment with LA (Figure 1).

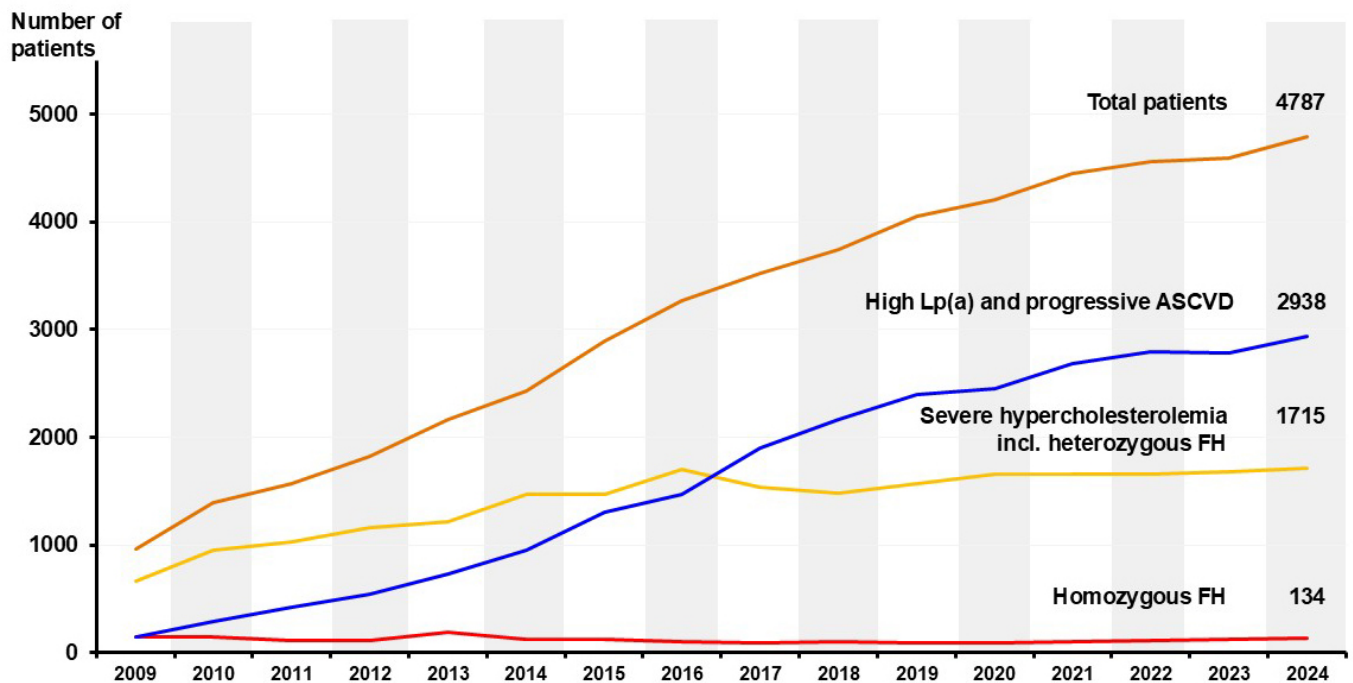


Figure 1. Development of the number of LA patients in Germany since 2009. The figures were taken from the annual quality reports of the National Association of Statutory Health Insurance Physicians and the regional Associations of Statutory Health Insurance Physicians^[18]. No official figures are available for the time before 2009. The graph depicts total LA patients and stratified figures according to the three indications for LA in the German reimbursement guidelines, which have been in effect since 1991, and 2008 respectively^[11,12]. The latest figures, representing the status as of December 31, 2024, were published in 2026. LA: lipoprotein apheresis; Lp(a): lipoprotein(a); ASCVD: atherosclerotic cardiovascular disease; FH: familial hypercholesterolemia.

LA patients in the Pro(a)LiFe study, which is described below in detail, had been characterized regarding apo(a) genotypes and phenotypes^[13,19]. A high frequency of patients with small apo(a) isoforms was found, which are generally associated with increased Lp(a) concentration and ASCVD risk. 95.3% of patients expressed at least one small apo(a) isoform. This figure is four times higher than the 23.6% observed in a large sample of over 6,000 subjects from two population-based studies in Germany^[20]. The frequency of Lp(a) risk alleles tagged by the single-nucleotide polymorphisms (SNPs) rs3798220 and rs10455872 was significantly higher in Pro(a)LiFe patients^[9,21]. However, 35.2% of clinically recognized Pro(a)LiFe patients with a small apo(a) phenotype were not tagged by either SNP. At the individual level, the smaller allele was strongly associated with being the major isoform in plasma. While small isoforms accounted for the high Lp(a) level in most patients, large isoforms were solely responsible for the elevated Lp(a) in a few cases (4.7% of patients); however, patients were clinically indistinguishable. These results confirmed that adding isoform-associated markers or SNPs does not improve the criteria for refinement of the Lp(a)-HLP-associated progressive ASCVD phenotype, as revealed by clinical and imaging techniques.

A systematic screening process for these patients is not in place throughout Germany. The identification of patients is contingent upon the existence of networks of nephrologists who possess expertise in LA treatment and cardiologists who are involved in the broader dissemination of knowledge regarding Lp(a) testing. This circumstance has led to a persistent increase in the overall number of LA patients, particularly those with the Lp(a) indication, since 2009 (Figure 1). The introduction of PCSK9 inhibitors in 2015 did not result in a decrease in the number of patients receiving LA due to severe hypercholesterolemia, thereby documenting the persistent need for this treatment option for this patient population.

3. Progression Is an Important Feature of the ASCVD Risk Conferred by Lp(a)

The UK Biobank was a pivotal resource in precisely characterizing the Lp(a)-associated ASCVD risk based on a substantial sample of 460,506 middle-aged UK Biobank participants, with a median follow-up of 11.2 years^[1,2,22]. The threshold concept could not be applied to the relationship between Lp(a) concentrations and cardiovascular risk, suggesting a continuous relationship instead. Lp(a)

concentrations have been demonstrated to serve as a predictor of incident ASCVD among middle-aged adults in both primary and secondary prevention contexts, with a linear gradient in risk across the distribution^[22]. Examination of the relative risk increase in relation to Lp(a) concentrations revealed a continuous risk increase ranging from 1.22-fold to 2.72-fold at concentrations ranging from 30 mg/dL to 150 mg/dL^[2], as compared to those with the median Lp(a) concentration of 7 mg/dL.

For practical reasons, the 2022 EAS consensus statement concluded that Lp(a) concentrations of up to 30 mg/dL do not pose a significant clinical risk. Concentrations above 50 mg/dL however, have been associated with a clinically relevant risk increase. The range of 30 to 50 mg/dL is considered to be a gray zone^[1,2,23]. It is important to note that these risk estimates reflect disease rates in the context of contemporary clinical practice, including recommended screening procedures and therapeutic interventions for preventing ASCVD. Similarly, a contemporary US cohort study of over 16,000 individuals with an extended follow-up period of 11.9 years demonstrated that elevated Lp(a) levels were independently associated with MACE in individuals with and without baseline ASCVD^[24].

The particular risk for future cardiovascular events in those with established coronary artery disease was investigated across various settings. Using prospective serial coronary computed tomography angiography with a 10-year scan interval, it was demonstrated that higher Lp(a) levels were associated with increased progression of coronary plaque burden^[25]. Furthermore, Lp(a) was associated with increased prevalence of low-density noncalcified plaque and peri-coronary adipose tissue inflammation. Based on 273,770 US individuals with baseline ASCVD, higher Lp(a) levels were associated with continuously increasing risk of a recurrent ASCVD event regardless of sex and ethnicity^[26]. Lp(a) concentrations were independently associated with subsequent recurrent events following an acute coronary syndrome (ACS) in a Chinese cohort of 931 patients with 1–2 years of follow up and in the Multi-Ethnic New Zealand Study of Acute Coronary Syndromes (MENZACS) with 1,900 patients enrolled during their ACS admission and median follow-up of 4.9 years^[27,28]. Hospitalisation with a first ACS is a critical opportunity to reassess all risk factors, including Lp(a). Risk reduction should include Lp(a) as a target for secondary prevention^[27].

For stable chronic coronary syndromes (CCS), several studies demonstrated the impact of Lp(a) concentration on recurring events. A study cohort again from the UK Biobank included 32,537 incident ASCVD patients; 5,204 with elevated (median 209.9 [IQR 174.6–258.6] nmol/L) and 22,257 with normal Lp(a) (median 12.5 [IQR 5.7–25.43] nmol/L). Within the first year of follow-up, the incidence rates of composite MACE were significantly higher in patients with elevated versus normal Lp(a)^[7]. This trend was also observed in the median 4.7-years follow-up. A significant association between Lp(a) concentration and future cardiovascular events was shown in 7,863 patients with stable CCS during 6 years' median follow-up in the Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) study, a sub-study of the Treating to New Targets (TNT) study, which was a randomized trial that compared the efficacy of high (80 mg) versus low (10 mg) dose atorvastatin for the secondary prevention of coronary artery disease^[29]. After adjusting for age, sex and treatment arm, plasma levels of Lp(a) among other markers were predictive of recurrent major cardiovascular events^[30]. The findings were attributable particularly to effects in those with the highest Lp(a) decile of > 73 mg/dL. In a Chinese real-world study with a sample size of 7,562 patients with established coronary artery disease under secondary prevention therapy and mean follow-up of 5 years gave further evidence that Lp(a) is independently associated with the risk of recurring ASCVD events^[31].

The absolute risk is contingent upon the global risk, which encompasses not only Lp(a) concentrations but also the risk derived from conventional risk factors, including age, sex, blood cholesterol, blood pressure, smoking, diabetes, family history of heart attacks in early life, and BMI^[23]. Two individuals with an identical high Lp(a) concentration of 150 mg/dL exhibit an absolute risk of approximately 14% or 68%, depending upon their baseline risk profile. This huge discrepancy in absolute risk can be attributed to the presence of either a 5% baseline risk, indicative of an absence or minimal presence of conventional risk factors, or a 25% baseline risk, signifying a substantial number of traditional risk factors. Population samples from the UK Biobank revealed that the risk associated with Lp(a) was attenuated among individuals with preexisting ASCVD, compared to those without ASCVD at baseline related to statin use^[22]. Consequently, Lp(a)-associated risk can be mitigated by the use of escalating targeted LDL-C-lowering therapy^[26]. Therefore, the reduction of modifiable traditional risk factors is the ultimate goal in case of elevated Lp(a) concentrations to decrease the global risk of a given person as well as the individual relative Lp(a) associated risk.

4. The Pro(a)LiFe Study

Without the option of a controlled trial, the best way to generate new prospective data to fulfill demands of the G-BA in 2008 was a prospective observational study comparing the incidence rates of cardiovascular events in patients with Lp(a)-HLP and progressive ASCVD retrospectively before and prospectively after commencing chronic LA. The Pro(a)LiFe study was designed accordingly with follow-up reports after two, five and 12 years of regular LA treatment^[12,19,32]. In addition, the Pro(a)LiFe cohort was compared to corresponding clinical trajectories of the above mentioned well-characterized UK-Biobank cohort (UKBBC) with incident ASCVD and verified risk enhancement due to elevated Lp(a)^[7,32].

In the Pro(a)LiFe study cardiovascular event rates were investigated over a total trajectory of 17 years in 170 consecutive patients of White ethnicity before and after start of regular LA as treatment of high Lp(a) associated with progressive ASCVD according to German reimbursement guidelines (Figure 2). Patients were enrolled in 2008 to 2010. Patients had established early ASCVD including a positive

family history in first-degree relatives in 59.4% with a median of two previous cardiovascular events reflecting the exceptional selectivity of the Pro(a)LiFe population^[12,19,32]. Patients experienced the development of progressive ASCVD over a period of 5 years prior to initiation of LA treatment despite maximal treatment of all other cardiovascular risk factors including LDL-C. 154 patients (90.6%) completed 5 prospective study years, and 129 (76.6%) still received well tolerated regular LA at year 12. LA treatment frequency varied between twice per week to every three weeks, with weekly being the major schedule in 93% in year 1 and 86% in year 12. Peripheral veins remained the vascular access route in > 70% of patients. Mean Lp(a) prior to regular LA was 108 mg/dL and was reduced on average by 67–68% per single LA treatment. Individual pre-LA Lp(a) concentrations did not change significantly over the follow-up period. Mean LDL-C at baseline and before LA treatments remained at 99–102 mg/dL (2.7–2.8 mmol/L) during years 1–5, yielding an interval mean of 84 mg/dL (2.2 mmol/L). Introduction of PCSK9-inhibitors and bempedoic acid after year 5 resulted in a significant decline in pre-LA LDL-C during years 6 to12, averaging 82 mg/dL (2.1 mmol/L) with an interval mean of 67 mg/dL (1.7 mmol/L). Mean LDL-C reduction rates were 66–68%. Lipid-lowering drug use remained consistently high (95.3% at first LA; 94.8% at year 12).

The primary composite clinical endpoint of the Pro(a)LiFe study was the mean annual rate of cardiovascular events per patient, separated as MACE (major adverse cardiac event) and ACVE (events in any vascular territory). No conclusions were possible regarding aortic valve pathologies due to the very low number of affected patients. Median course of the pre-LA period and mean annual rates of MACE and ACVE during 17 study years are depicted in Figure 2^[32]. The median observation period revealed that the ASCVD diagnosis was made three years prior to the onset of the progressive phase. Initiation of regular LA was associated with rapid stabilization of the progressive ASCVD that had developed in the 5 years preceding treatment. Annual mean event rates for MACE and ACVE were 78% and 75% lower, respectively, during chronic LA compared to the pre-LA progressive phase. Coronary artery disease-related events represented 72% of all events during years -5 to -1, and 62% during years +1 to +12. The significant LDL-C reduction achieved after year 5 through PCSK9-inhibitors and bempedoic acid was not correlated with any further change in mean annual event rates, confirming the primary therapeutic importance of Lp(a) elimination.

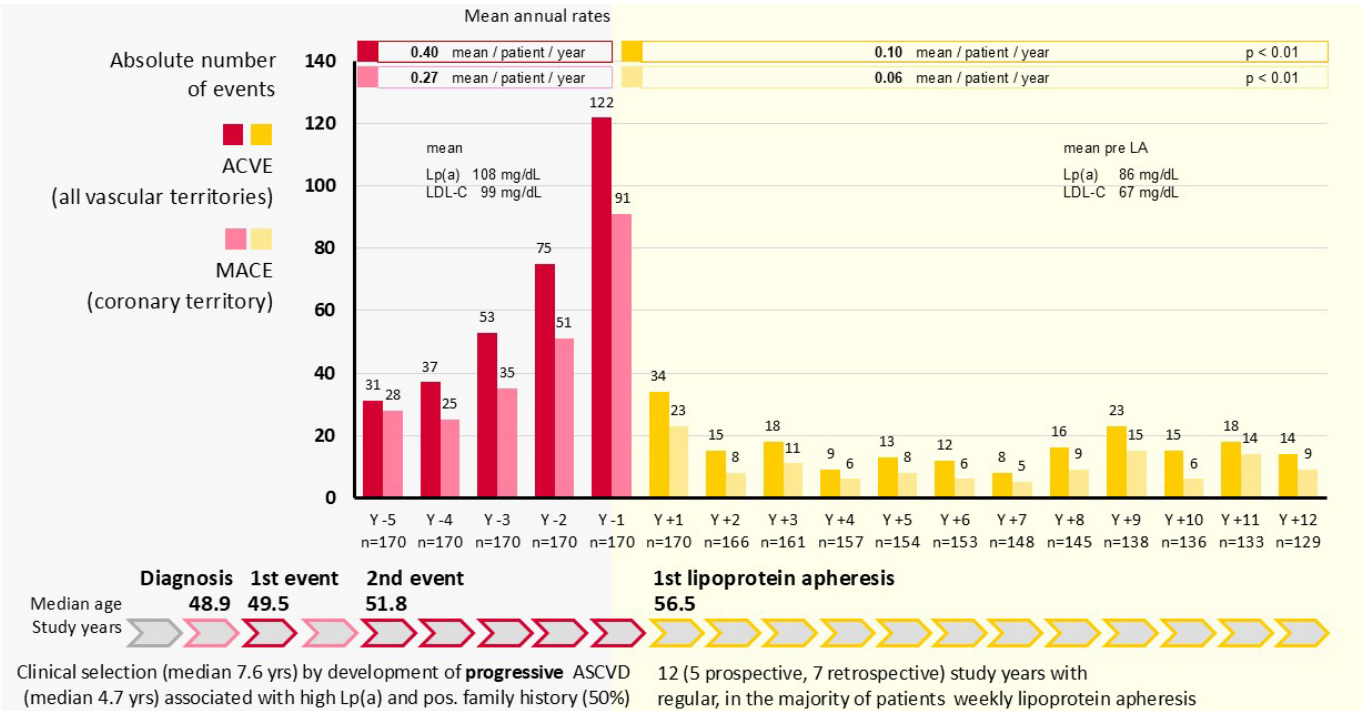


Figure 2. 17 years trajectory of the Pro(a)LiFe study with absolute numbers of events (MACE or ACVEs in all vascular beds)^[32]. MACE was defined as cardiovascular death, non-fatal MI, coronary bypass surgery, PCI or stent. ACVE were defined as the sum of all documented cardiac or vascular events in arterial vascular beds, i.e. MACE (see above), or cerebrovascular event [non-hemorrhagic, cerebrovascular event = TIA or PRIND or ischemic stroke or carotid PTA or carotid surgery] or peripheral vascular event [peripheral vascular event of lower extremities or renal arteries = PTA, stent, bypass surgery, amputation] or venous thrombotic event = deep venous thrombosis or pulmonary embolism. Due to the state of discussion in 2008 venous thrombotic events had been included in the original study protocol^[12,19]. MACE: major adverse cardiac event; ACVEs: adverse cardiac or vascular events; PCI: percutaneous coronary intervention; TIA: transient ischemic attack; PRIND: prolonged reversible ischemic neurologic deficit; PTA: percutaneous transluminal angioplasty; MI: myocardial infarction; ASCVD: atherosclerotic cardiovascular disease.

The UKBBC for comparative analysis was stratified by low and high Lp(a) concentrations, defined as < 65 nmol/L (< 30 mg/dL; n = 22,257) versus >150 nmol/L (> 70 mg/dL; n = 5,204), with the high-concentration group exhibiting a range resembling that of the Pro(a)LiFe study^[17,32]. Incidence rates per 100 patient-years were directly comparable between studies, as both included recurrent

events. ASCVD in the UKBBC was defined as established coronary artery disease, cerebrovascular disease, and peripheral artery disease (PAD); PAD served as index diagnosis only and was excluded from follow-up incidence rates. Comparisons between Pro(a)LiFe and UKBBC therefore relate to the composite of MACE plus ischemic stroke (IS). The UKBBC median follow-up of 4.7 years corresponded well with Pro(a)LiFe's 5-year retrospective and prospective follow-up periods.

Before beginning LA, the Pro(a)LiFe cohort's rates of the primary composite of MACE plus IS were significantly higher than those of both UKBBC subgroups one year after their first ASCVD event (Figure 3). After one year of LA treatment, event rates declined significantly. For the primary composite of MACE plus IS rates fell significantly below both UKBBC subgroups one year after their first ASCVD event. Over the full 5-year period after LA initiation, event rates remained significantly lower than both UKBBC subgroups for MACE plus IS compared to the UKBBC's corresponding median follow-up of 4.7 years. In Pro(a)LiFe, cardiovascular mortality was 2.9% after year 5, and 10.0% after year 12. In the UKBBC, cardiovascular mortality was 8.6% and 8.8% for the normal and elevated Lp(a) subgroups at median follow-up.

Following LA initiation, Pro(a)LiFe event rates changed to a level significantly below those of the UKBBC subgroups with low as well as with elevated Lp(a). The main baseline differences between Pro(a)LiFe and UKBBC were higher LDL-C concentrations and lower prevalence of lipid-lowering medication in the UKBBC. Data on lipid-lowering therapy during UKBBC follow-up were unavailable, however, intensification of lipid lowering therapy can be assumed after the incident ASCVD events.

5. The German Lipoprotein Apheresis Registry (GLAR)

GLAR was established in 2012, providing 13 years of real-world data on lipoprotein apheresis (LA) treatment at the time this manuscript was compiled^[9]. GLAR remains a voluntary registry, so data completeness depends on the ongoing engagement of participating centers. All patients in the registry were approved for regular LA therapy according to German reimbursement guidelines, namely elevated LDL-C and/or Lp(a) and progressive ASCVD, despite prior use of maximally tolerated lipid-lowering therapy. Over 2,300 patients undergoing well tolerated regular LA therapy for hypercholesterolemia and/or high Lp(a) with progressive ASCVD were enrolled.

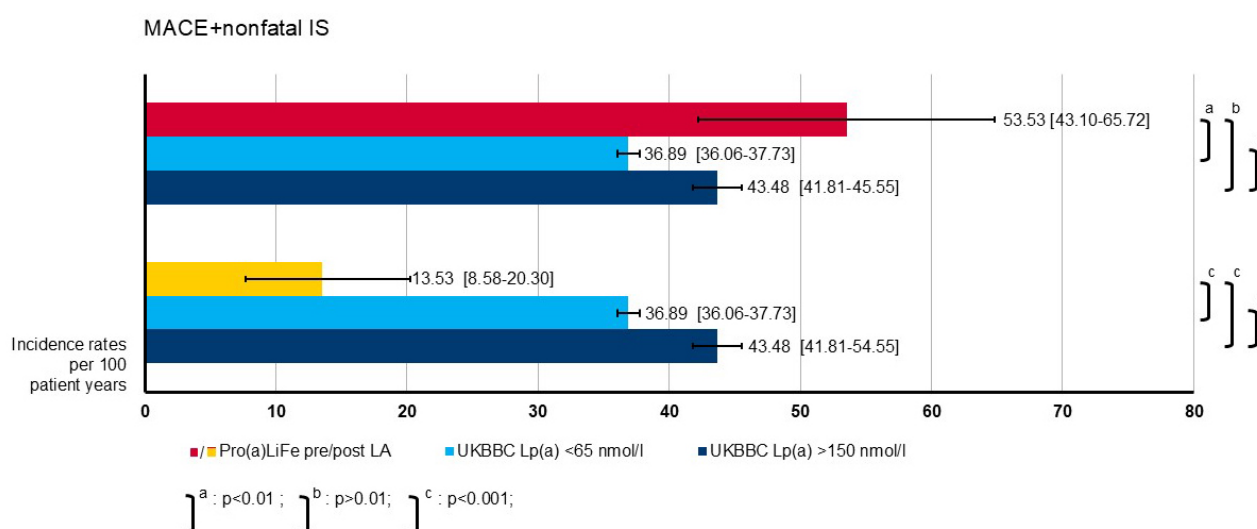


Figure 3. Comparison of incidence rates of MACE plus non-fatal IS per 100 patient years of Pro(a)LiFe patients and the UKBBC stratified by Lp(a) concentrations < 65 nmol/L (> 30 mg/dL) and > 150 nmol/L (> 70 mg/dL)^[32]. Bars depict the one-year intervals before and after commencing regular LA for Pro(a)LiFe patients and the one-year interval after the incident ASCVD event for UKBBC cohorts. MACE: major adverse coronary events; IS: ischemic stroke; UKBBC: UK Biobank Cohort; ASCVD: atherosclerotic cardiovascular disease.

LA demonstrated substantial and immediate median reductions in LDL-C and Lp(a) levels of at least 70%. After initiation of LA, event rates due to ASCVD in coronary and other vascular territories were rapidly changed, with a mean annual rate difference of > 70%, in a range ≤ 0.1 essentially identical to the Pro(a)LiFe study^[9]. The reduction in cardiovascular events was most pronounced during the first year of weekly LA treatment compared to the year before LA initiation, with event rates declining further or remaining persistently low in subsequent years^[9]. This was observed in patients treated for severe hypercholesterolemia as well as in patients treated for high Lp(a). Adverse events remained infrequent and were primarily related to vascular access complications. The introduction of PCSK9 inhibitors has had only a limited impact on ongoing LA therapy within the registry cohort. Overall, these findings provide robust, real-world evidence supporting the clinical benefits of regular LA therapy for this high-risk patient population.

6. Effects of Lipoprotein Apheresis Beyond Lipoprotein Elimination

The major clinical benefit of LA is the prevention of cardiovascular events. LA has been shown to rapidly remove apoB-containing atherogenic lipoproteins, including Lp(a) with its load of oxidized phospholipids (oxPL), from plasma through pulsed physical extracorporeal elimination. Subsequently, Lp(a) is replaced by endogenous nascent Lp(a). The association of oxidized phospholipids (oxPLs) with small apo(a) isoforms is regarded as a key determinant of Lp(a)-mediated ASCVD risk^[33]. As a clinical correlate to these basic investigations, oxPLs measured on apo B-100, which primarily reflect the content of oxPLs on Lp(a), strongly predict ASCVD.

Coronary microvascular dysfunction (CMD) is increasingly recognized as a central mechanism underlying myocardial ischemia and adverse cardiovascular outcomes in patients with and without obstructive coronary artery disease^[34]. The coronary microcirculation plays a critical role in regulating myocardial perfusion through the concerted action of myogenic, metabolic, and endothelial pathways. The disruption of these mechanisms results in impaired vasodilatory capacity, abnormal coronary flow reserve, and microvascular ischemia. The pathophysiologic mechanisms underlying CMD include endothelial dysfunction, structural remodeling, inflammation, and neurohormonal dysregulation. Although the pathogenesis of ASCVD is multifactorial, lipoprotein-induced endothelial injury and dysfunction may play an important role in the development of atherosclerosis.

Elevated levels of lipoprotein (a) have been demonstrated to be associated with a selective impairment of the vasodilator capacity of receptor-mediated endothelial stimuli, such as acetylcholine. This association has been observed even in cases where atherosclerotic lesions were not recognizable by angiography^[35,36]. The association of elevated levels of Lp(a) with reduced apo(a) sizes has been observed to be concomitant with endothelial dysfunction^[37]. A single LA treatment has been shown to enhance endothelium-dependent vasodilation, and the elimination of oxidized Lp(a) may play a pivotal role in this process^[8,38,39]. An early observation with LA was that, after a few LA treatments at weekly intervals, patients with coronary artery disease reported significantly reduced episodes of angina pectoris, which had previously been resistant to conventional therapy^[40]. LA methods, particularly those that result in significant fibrinogen reduction in addition to LDL, such as double filtration plasmapheresis (DFPP) and HELP apheresis, have been shown to enhance rheological properties and augment oxygen supply to previously insufficiently perfused or ischemic myocardium^[41]. The restoration of endothelial function by rapid lipoprotein lowering results in an improved vasomotor response to endogenous vasodilative substances, thus explaining the clinical improvement. Recent investigative findings have corroborated the hypothesis that LA engenders a prompt enhancement in coronary microvascular function, thereby augmenting myocardial perfusion and restoring endothelial-dependent vasodilation to its normal state^[42]. In a randomized, crossover trial including patients with elevated Lp(a), three months of weekly LA proved to be an effective treatment for patients with refractory angina. This treatment resulted in improvements in myocardial perfusion, atheroma burden, exercise capacity, and angina symptoms^[43].

Endothelial dysfunction is a significant indicator of early arterial damage. Elevated levels of Lp(a) in the coronary circulation may suggest a crucial role for Lp(a) in the development of atherosclerosis and its potential contribution to the pathogenesis of myocardial ischemia. Endothelial dysfunction associated with elevated Lp(a) levels may contribute to the pathogenesis of myocardial ischemia, thus exacerbating lipoprotein triggers of ASCVD development and progression.

It is widely accepted that the primary cause of the majority of acute coronary syndromes is the erosion of a coronary artery's superficial layer, accompanied by the rupture of a plaque's fibrous cap^[44]. A fibrous cap generally envelops a lipid-rich center, which is also referred to as the necrotic core. Ruptured plaques are characterized by the presence of substantial lipid cores and a significant presence of inflammatory cells. It has been postulated that the improvement of plaque morphology at the tissue level could serve as an additional mechanism through which LA prevents clinical events. This process entails a quantitative reduction in the number of vulnerable plaques and a qualitative limitation of their propensity to rupture^[44,45].

7. Lipoprotein Apheresis and Novel Lp(a) Lowering Drugs

There is a fundamental difference between LA and drugs regarding the reduction effect on lipoproteins particularly Lp(a). The immediate approximately 70% physicochemical elimination of Lp(a) particles following the LA session is accompanied by a subsequent return to baseline levels after approximately one week before the next treatment, thereby generating a sawtooth-like pattern of concentration changes with a time averaged mean reduction of 30-35% between LA sessions. Conversely, drug treatment leads to a constant decline in Lp(a) concentration, with the rate of decline contingent upon the drug's mechanism of action and half-life.

Among the established lipid-lowering therapies, only PCSK9 inhibitors, alirocumab, evolocumab, and inclisiran, were shown to significantly decrease Lp(a) levels. However, the effects of these drugs are modest, achieving reductions of Lp(a) of approximately 20-30% with hypothetical clinical significance^[46]. The additional ability to lower high Lp(a) concentrations was also shown for enlicitide, an oral PCSK9 inhibitor, the approach of PCSK9 gene editing, and obicetrapib, a cholesterol ester transfer protein inhibitor^[3,47,48]. However, none of these novel drugs are yet testing whether non-specifically lowering Lp(a) concentrations reduces the ASCVD risk.

Apolipoprotein(a) is synthesized exclusively in hepatocytes, making hepatic production a primary target for therapeutic intervention

to lower Lp(a) concentration^[49]. Advances in therapeutics targeting hepatic mRNA to inhibit protein synthesis have enabled the development of several potent, specifically Lp(a)-lowering therapies^[50]. Antisense oligonucleotides (ASOs) directed to the hepatocyte for targeting the mRNA of the *LPA* gene (Pelacarsen), and small-interfering RNAs (N-acetylgalactosamine-conjugated siRNAs: Olpasiran, Zerlasiran, and Lepodisiran) have become available. Muvalaplin is a small molecule inhibitor of Lp(a) synthesis that prevents the interaction of apo(a) and apolipoprotein B-100 (apoB-100), which is necessary for the formation of Lp(a). Lp(a) is formed by the covalent di-sulphide linkage of a molecule of apo(a) to a molecule of apoB-100 on an LDL-like particle. In contrast to other Lp(a)-lowering therapies under development, which require subcutaneous injections, muvalaplin is a daily oral medication. The maximum Lp(a) reductions that have been reported according to standard apo(a)-based assays are 80% for Pelacarsen, > 90% for Olpasiran, Zerlasiran, and Lepodisiran, and 69% for Muvalaplin, which showed 86% reduction in an intact Lp(a) assay^[3,50]. Pelacarsen, Olpasiran, Lepodisiran, and Muvalaplin are being studied in Phase 3 cardiovascular outcomes trials aiming at drug approval^[50].

Beyond these pharmacodynamic and mechanistic differences, LA and Lp(a)-targeting drugs differ substantially in their clinical positioning. Given the invasive nature of an extracorporeal apheresis treatment, and in accordance with the 2008 G-BA reimbursement criteria that require documentation of progressive ASCVD despite maximally tolerated lipid-lowering therapy, LA is initiated after an ASCVD event and functions as a late-line treatment option for a narrowly defined, very high-risk subgroup (Figure 4).

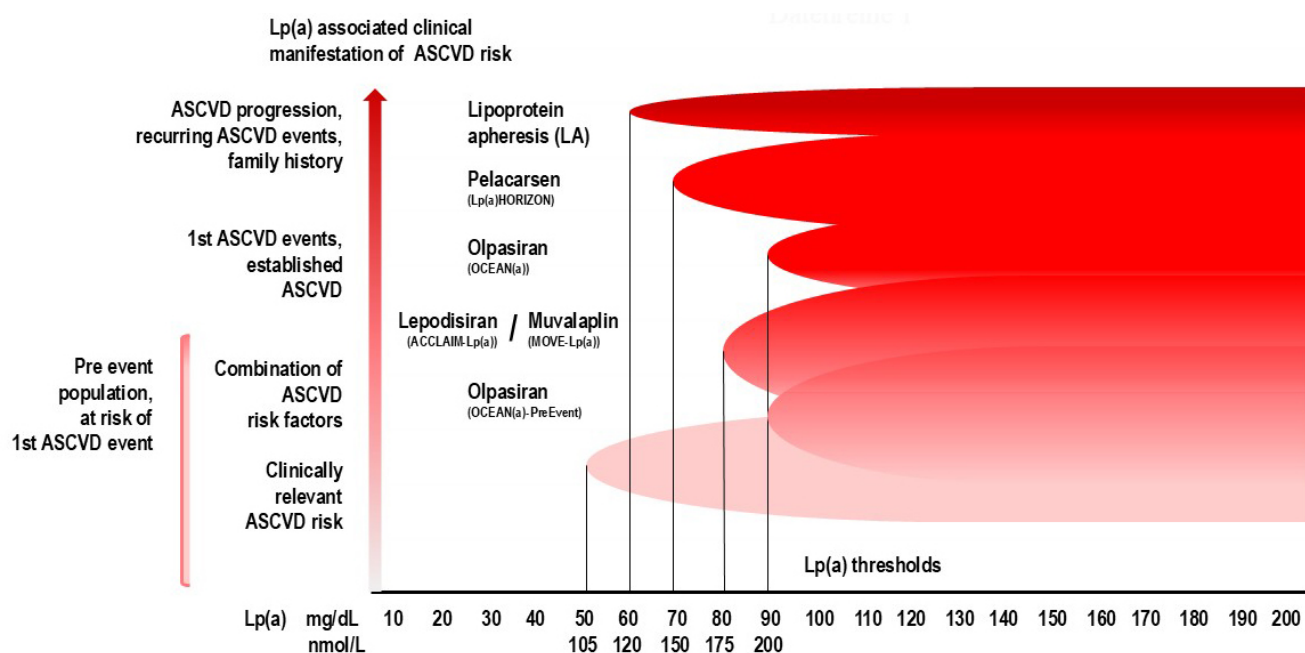


Figure 4. The illustration depicts the intersecting domains determined by Lp(a) concentration and the increasing severity of clinical Lp(a)-associated ASCVD risk. According to the German reimbursement guideline and the inclusion criteria of Phase 3 trials of Lp(a) lowering drugs, the potential candidates for these treatments encompass a wide range of elevated Lp(a) concentrations and a broad scope of ASCVD risk (Table 1). All Lp(a) thresholds are above 50 mg/dL (105 nmol/L), which is regarded as the area of clinically relevant Lp(a) associated risk. The broadest area even including the pre-event population is covered by Olpasiran with the OCEAN(a)-PreEvent trial, Lepodisiran, and Muvalaplin, followed by Pelacarsen and Olpasiran with the OCEAN(a) trial, while LA is limited to the smallest, most extreme area of Lp(a) associated with the clinical manifestation of ASCVD risk. Lp(a): lipoprotein(a); ASCVD: atherosclerotic cardiovascular disease; LA: lipoprotein apheresis.

Conversely, certain Phase 3 programs of novel Lp(a)-targeting drugs do include patients without a prior event (Table 1, Figure 4). While established ASCVD remains a common inclusion criterion, as in Lp(a)HORIZON (Pelacarsen) and OCEAN(a) (Olpasiran), the ACCLAIM-Lp(a) (Lepodisiran) and MOVE-Lp(a) (Muvalaplin) trials additionally enroll high-risk individuals without a prior ASCVD event, for example those with established CAD, carotid stenosis, PAD, a high coronary artery calcium score, or combinations of risk factors. OCEAN(a)-PreEvent (Olpasiran) extends this approach the furthest into primary prevention, enrolling individuals aged ≥ 50 years with Lp(a) ≥ 200 nmol/L and multiple ASCVD risk factors and/or evidence of atherosclerosis potentially just by imaging techniques. Notably, the study explicitly excludes patients with a prior acute atherothrombotic event or prior or planned arterial revascularization (Table 1).

Progressive ASCVD is an exceptional feature of the Pro(a)LiFe patients and fundamental for approval within the German reimbursement guideline. However, it is not explicitly included in the Phase 3 clinical trial inclusion criteria for evaluating novel drugs for specific Lp(a) lowering (Table 1). Thus, it is crucial to evaluate whether the results of these trials can be generalized to patients who fulfill the German reimbursement requirements. A comparison of the baseline characteristics of the patients of the Pro(a)LiFe, the UK Biobank cohort, and the Lp(a)HORIZON study, the first of the Phase 3 trials with published baseline characteristics,

reveals considerable similarities (Table 2).

Table 1. The indication of lipoprotein apheresis as outlined in the 2008 German reimbursement regulation^[11] and major characteristics of randomized controlled Phase 3 trials of drugs specifically lowering Lp(a). Trial information according to the ClinicalTrials.gov registry (<https://clinicaltrials.gov/>, accessed June 1, 2026). Factor 2.15 was used for conversion of mg/dl into nmol/l, according to Welsh *et al.*^[7].

	Lipoprotein Apheresis	Pelacarsen Lp(a)HORIZON (NCT04023552)	Olpasiran OCEAN(a) (NCT05581303)	OCEAN(a)-PreEvent (NCT07136012)	Lepodisiran ACCLAIM-Lp(a) (NCT06292013)	Muvalaplin MOVE-Lp(a) (NCT07157774)
Indication according to German reimbursement regulation since 2008	Lp(a) > 60 mg/dL (as equivalent > 120 nmol/L) <u>Isolated</u> * Lp(a)-elevation and LDL-C in <u>normal range</u> **, and <u>progressive</u> *** cardiovascular disease (coronary, peripheral, cerebrovascular) as revealed clinically and by imaging techniques.	Lp(a) ≥ 70 mg/dL (per protocol) (≥ 150 nmol/L ^[51]) Age ≥ 18 years and established ASCVD (myocardial infarction or ischemic stroke ≥ 3 months from screening, ≤ 10 yrs prior to screening, or peripheral artery disease. Optimized LDL-C lowering and other risk factor treatment at randomization.	Lp(a) ≥ 200 nmol/L (per protocol) (~90 mg/dL by conversion) Age ≥ 18 years and history of ASCVD (myocardial infarction and/or coronary revascularization and at least 1 additional risk factor). Optimization of ASCVD risk 3 months prior to randomization.	Lp(a) ≥ 200 nmol/L (per protocol) (~90 mg/dL by conversion) Age ≥ 50 years and multiple ASCVD risk factors, and/or evidence of atherosclerosis, no prior ASCVD event (myocardial infarction, stroke, transient ischemic attack, acute limb ischemia, prior or planned arterial revascularization). Optimization of ASCVD risk prior to randomization.	Lp(a) ≥ 175 nmol/L (per protocol) (~80 mg/dL by conversion) Adult ≥18 years with established ASCVD with an event or revascularization > 60 days before screening; or ≥ 55 years who are at risk for a first ASCVD event and established CAD, carotid stenosis or PAD without prior revascularization; diagnosis of FH; or a combination of high-risk factors. Stable regimen of lipid lowering therapy as well as control of hypertension and diabetes.	Lp(a) ≥ 175 nmol/L (per protocol) (~80 mg/dL by conversion) Adult ≥18, ASCVD event within 10 years prior to screening (MI, stroke, coronary or peripheral revascularization); or risk for first ASCVD event due to established CAD, carotid-stenosis, PAD, or high CAC score; impaired renal function associated with Dm; or combinations of high-risk factors with exclusion of severe kidney impairment. Stable regimen of lipid lowering therapy as well as control of hypertension and diabetes.
Inclusion criteria of phase 3 trials (brief summary)						
Treatment regimen	Weekly, 3-4 hours	Monthly, s.c.	Every 3 months, s.c.	Every 3 months, s.c.	Every 6 months, s.c.	Daily, oral
Primary outcomes	n.a.	Reduction of the risk of expanded MACE (cardiovascular death, non-fatal MI, non-fatal stroke and urgent coronary revascularization requiring hospitalization).	Time to CHD death, MI, or urgent coronary revascularization.	Time to CHD death, MI, or urgent coronary revascularization, whichever occurs as patients' first MACE.	Time to first composite MACE (cardiovascular death, nonfatal MI, nonfatal ischemic stroke, urgent revascularization).	Time to first composite MACE (cardiovascular death, nonfatal MI, nonfatal ischemic stroke, urgent revascularization).
Estimated study completion	n.a.	June 2026	March 2028	October 2031	March 2029	March 2031
Enrolment	n.a.	8323 (actual)	7297 (actual)	11000 (estimated)	17300 (estimated)	10450 (estimated)

*isolated: optimized treatment of all other cardiovascular risk factors; **normal range: close to contemporary ESC target levels; ***progressive: to be validated by clinical case review including family history, and by imaging techniques; ASCVD: atherosclerotic cardiovascular disease; CAD: coronary artery disease; CHD: coronary heart disease; FH: familial hypercholesterolemia; LDL-C: low density lipoprotein cholesterol; ESC: European Society of cardiology; Lp(a): Lipoprotein(a); MACE: major cardiovascular event; MI: myocardial infarction; PAD: peripheral artery disease.

Table 2. Characteristics of the patients enrolled in the Pro(a)LiFe study at baseline and year 12, the UK Biobank cohort with Lp(a) > 150 nmol/L at baseline, and the Lp(a)HORIZON study at baseline^[7,12,32,51].

	Pro(a)LiFe baseline	Pro(a)LiFe year 12	UK Biobank, Lp(a) > 150 nmol/l baseline	Lp(a)HORIZO baseline
<i>n</i>	170 (enrolled)	120 (still in trial)	5,204 (enrolled)	8,323 (enrolled)
Age (years, mean)	56.5 (10.8)	66.6 (9.9)	66.1 (7.2)	59.7 (10.0)
Male, <i>n</i> (%)	123 (72.3%)	110 (71.4%)	2,941 (56.5%)	6,079 (73%)
Ethnicity				
white	170 (100%)	120 (100%)	4,956 (95.2%)	6,505 (78.2%)
black	-	-	91 (1.7%)	302 (3.6%)
asian	-	-	93 (1.8%)	1,339 (16.1%)
other	-	-	61 (1.2%)	176 (2.1%)
BMI, kg/m ² , mean	27.3 (3.9)	27.7 (4.8)	28.4 (4.9)	28.3 (5.1)
Hypertension	125 (73.5%)	106 (88.4%)	3,014 (57.9%)	5,909 (71.0%)
Diabetes mellitus	37 (21.8%)	28 (23.3%)	710 (13.6%)	2,081 (25.0%)
Current smoker	8 (4.7%)	0	782 (15.0%)	1,184 (14.2%)
Lp(a) median (Q1-Q3), mg/dL	103.5 (80.6-130.0)	98.0 (74.0-132.5)	96.4 (93.6-118.7)	108.2 (86.6-137.8)
median (Q1-Q3), nmol/L*	222.5 (173.3-279.5)	210.7 (159.1-284.9)	209.9 (174.6-258.6)	235.7 (203.5-307.7)
mean (SD), mg/dL	108.1 (46.1)	105.2 (41.7)	102.9 (18.6)**	110.9 (37.9)**
mean (SD), nmol/L*	232.4 (99.1)	226.2 (89.7)	214.4 (62.2)**	249.0 (77.2)**
< 90 mg/dL	61 (35.9%)	54 (45.0%)	-	1,782 (21.4%)
≥ 90 mg/dL	98.9 (38.4)	66 (55.0%)	-	6,540 (78.6%)
LDL-C				
median (Q1-Q3), mg/dL	90.0 (71.0-118.0)	79.0 (62.0-99.0)	-	64.6 (52.0-80.8)
mean (SD), mg /dL	98.9 (38.4)	81.8 (32.1)	144.4 (38.9)	65.8 (21.3)**
High intensity statin	154 (90.5%)	94 (78.3%)	not reported	6,459 (77.5%)
Bempedoic acid	0	13 (10.1%)	not reported	not reported
Ezetimibe or bile acid binding resin	81 (47.6%)	71 (59.2%)	not reported	4,711 (56.6%)
PCSK9-inhibitor	0	17 (15.5%)	not reported	897 (10.8%)

*: conversion factor for mg/dL into nmol/l was 2.15 according to Welsh *et al.*^[7]; in Lp(a)HORIZON parallel measurements were performed with mass and molar calibration^[51];

** calculated using an approximation of Wan *et al.*^[52]; Lp(a): lipoprotein(a); LDL-C: low-density lipoprotein cholesterol; BMI: body mass index; SD: standard deviation.

Two distinct scenarios must be taken into consideration following the anticipated approval of Lp(a) lowering drugs: 1. initiation of regular LA in new patients or 2. continuation of ongoing regular LA. A recent study investigated continuation of ongoing regular LA due to high Lp(a) according to the German reimbursement guidelines^[53]. In a randomized fashion patients who had ≥ 35 LA sessions in the year before enrolment received monthly injections of 80 mg Pelacarsen. 48 patients completed the 52 weeks study protocol. LA was only performed after week one if the Lp(a) level was > 60 mg/dL at the previous visit before the scheduled next weekly LA. Such an experimental approach has never been considered for routine care. Median Lp(a) in the pelacarsen group was 90 mg/dL. The mean placebo-adjusted reduction of Lp(a) was 72%. With this regimen 69% of Pelacarsen treated patients had total avoidance of LA treatment defined as no single LA performed between week 12 and 52. The Lp(a)HORIZON trial is poised to yield substantial and clinically compelling results, which could lead to a notable decrease in the future incidence of new patients requiring LA and the potential requirement for Pelacarsen testing in patients already on regular LA treatment. Assuming the European approval of the new drug, the German Federal Joint Committee (G-BA) will be tasked with defining the detailed indication for the German reimbursement of the new drug. In addition, the G-BA might reevaluate the indication for LA for patients with high Lp(a) and progressive ASCVD.

The cost-effectiveness of lipid-lowering treatments is important for individual medical decisions as well as country-specific health economic evaluation. Modeling from the UK Biobank evaluated the treatment modifying effect of Lp(a) testing. From a societal

perspective, Lp(a) testing to reclassify ASCVD risk was cost-saving in Western European and North American countries^[54]. The Brussels International Declaration brought this matter on the international agenda^[55]. The potential for cost-effectiveness of drugs that target Lp(a) is contingent upon the favorable outcomes of Phase 3 trials, the characteristics of patients who are approved for treatment, and the actual cost. Costs and reimbursements for apheresis methods are generally highly variable internationally. Based on the available data, the cost-effectiveness of regular LA for patients with high Lp(a) levels and progressive ASCVD cannot be calculated. The 12-year update of the Pro(a)LiFe study indirectly addressed this issue^[32]. Comparing the mean annual MACE event rate in the last year of the progressive phase of ASCVD before initiation of regular LA with that during the 12-year regular LA from y+1 to y+12, the hypothetical number needed to treat (NNT) to halt the progression and stabilize the long-term clinical course was approximately 2.1, indicating high treatment efficacy. In this context, NNT provides a quick approach for estimating the relative efficacy of different treatments for clinical decisions and can be incorporated in health economic evaluation^[56]. Current reimbursement for weekly long-term LA is in the range of €45,000 per year. The specific selection process for patients involves many hurdles, including a critical assessment by health insurance companies before regular LA is approved, which exerts an additional overall cost-limiting effect. Since 2008, authorities in the German healthcare system have accepted the cost-effectiveness assumption of regular LA for these very high-risk patients. This subject might undergo a rigorous reevaluation as well.

8. Limitations of the Evidence

From a scientific perspective, the lack of adequate randomized controlled trials represents a significant limitation in the evaluation of the clinical benefits of lipoprotein apheresis for patients with high Lp(a) and progressive ASCVD. The absence of a parallel control group limits causal interpretation of event rate changes. Since LA eliminates Lp(a), LDL-C and other apoB containing atherogenic lipoproteins, it is not possible to disentangle to which extent clinical benefit is mediated solely by Lp(a) reduction. In addition to lipoprotein elimination, LA reduces plasma concentrations of proinflammatory and prothrombotic factors including oxidized phospholipids and fibrinogen, reduces blood viscosity, increases microvascular myocardial perfusion, and may provide beneficial effects on endothelial function. Only a randomized controlled trial could finally confirm the results of the 12-year follow-up of the Pro(a)LiFe trial as well as the observations made in the German Lipoprotein Apheresis Registry. As mentioned before, conduct of such a trial was not possible in the past, and it is not in sight in the future. Positive effects on treatment adherence exerted by weekly visits of patients to their LA center must also be mentioned in this context. However, all patients received maximally tolerated LDL-C-lowering drug treatment before their progressive ASCVD was identified as associated with Lp(a)-HLP; thus, supporting the hypothesis that lowering Lp(a) levels further reduced cardiovascular risk rather than just being associated with lower cardiovascular risk after commencing regular LA. Finally, there are pronounced differences across ethnicities with regard to Lp(a) levels and pathophysiological relevance of Lp(a). Therefore, conclusions on the putative clinical benefit of LA are valid only for white Europeans in the context of high Lp(a) being the indication.

9. Conclusion

The use of LA has been demonstrated to be an effective strategy for reducing plasma concentrations of atherogenic lipoproteins including Lp(a). A substantial body of evidence has accumulated from long-term experiences in Germany since 2008, including the results of the Pro(a)LiFe study, which, when considered in conjunction with the German Lipoprotein Apheresis Registry, substantiate the clinical efficacy of LA in the prevention of cardiovascular events associated with Lp(a) in very high risk patients with progressive ASCVD. The comparative analysis with the UKBBC was instrumental in addressing a significant evidence gap, which was attributable to the absence of a true control group in the Pro(a)LiFe study.

Novel highly potent medications specifically target the ASCVD risk of high Lp(a). Phase 3 clinical trials aim at approval of these drugs which offer greater ease of administration than LA. Translating the inclusion criteria of Phase 3 trials into recommendations for the use of these novel agents will present a significant challenge, particularly with respect to establishing Lp(a) thresholds and the range of clinical phenotypes for their indications. Expanding Lp(a) testing and treatment options for high Lp(a) are expected to have a significant population-level impact by facilitating the identification of individuals at exceptionally high risk and preventing a substantial number of cardiovascular events. The utilization of LA and pharmaceutical agents that specifically lower Lp(a) will provide a complementary therapeutic armamentarium.

Declarations

Authors contribution

Klingel R, Brandts J, Fassbender C, Heibges A: Conceptualization, methodology, writing-original draft, writing-review & editing.

Conflicts of interest

R. Klingel, C. Fassbender, and A. Heibges received research grants from Asahi Kasei Medical, Japan, and Diamed, Germany. J. Brandts has received research grants from Amgen, AstraZeneca, and Sanofi and speaker honoraria from Amgen, Berlin Chemie, Daiichi Sankyo, Menarini, Novartis, Novo Nordisk, and Sanofi. No other conflicts of interest to declare.

Ethical approval

Not applicable.

Consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

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