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Role of lipoprotein (a) in pathogenesis of ischemic heart disease, degenerative aortic stenosis, and heart failure

Vloga lipoproteina (a) v patogenezi ishemične bolezni srca, degenerativne aortne stenoze in srčnega popuščanja

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Abstract

Lipoprotein (a) [Lp (a)] is a well-established risk factor for atherosclerotic cardiovascular disease. Lp(a) shows unique proatherogenic and thrombogenic properties that are important in atherothrombosis, and its elevated concentrations have shown a causal relationship with an increased risk of myocardial infarction/ ischaemic heart diseases and stroke, independent of classical risk factors. Degenerative valvular aortic stenosis is the most prevalent valvular heart disease, and it shares common risk factors with ischaemic heart disease. Lp(a) has been shown to promote valve calcification and disease progression. A mechanistic link between Lp(a) and aortic stenosis was further confirmed in observational and genetic studies of patients with increased Lp(a) concentrations. On the other hand, the role of Lp(a) in the development of heart failure is less clear. Two polymorphisms of Lp(a), rs3798220 and rs10455872, have emerged as predictors of the development of heart failure. Lp(a)-related risk for heart failure is mostly associated with ischaemic heart disease and valvular aortic stenosis. However, the association of the rs3798220 polymorphism with heart failure can not be explained by either ischemic heart disease or valvular aortic stenosis. The present review aims to summarize and discuss the current state of the literature on pathophysiological and clinical aspects of Lp(a), with a focus on ischaemic heart disease, degenerative aortic valve stenosis, and heart failure.

Izvleček

Lipoprotein a [lipoprotein mali a, Lp (a)] je poznan in dobro raziskan dejavnik tveganja za aterosklerotične srčno-žilne bolezni. Lp (a) se s svojimi protrombogenimi in proaterogenimi lastnostmi pomembno vpleta v patogenezo ateroskleroze. Povišane koncentracije Lp (a) so se – neodvisno od ostalih dejavnikov tveganja – izkazale kot neodvisni napovedni dejavnik za miokardni infarkt oz. ishemično bolezen srca ter možgansko kap. Degenerativna aortna stenoza je najpogostejša bolezen zaklopk, povezana s podobnimi dejavniki tveganja kot ishemična bolezen srca. Povišane vrednosti Lp (a) igrajo pomembno vlogo tudi pri nastanku in napredovanju degenerativne aortne stenoze, saj Lp (a) sodeluje v procesu kalcificiranja zaklopke, ki je eden pomembnejših dejavnikov za razvoj bolezni. Patofiziološka vloga Lp (a) v nastanku degenerativne aortne stenoze pa se zrcali tudi v opazovalnih in genetskih raziskavah, v katerih so ugotovili, da so povišane vrednosti Lp (a) povezane z višjim tveganjem za stenozo aortne zaklopke. Nekoliko manj pa je jasna vloga hiperlipoproteinemije a pri razvoju srčnega popuščanja. Med polimorfizmi Lp (a) sta dva povezana z razvojem srčnega popuščanja (rs3798220 in rs10455872). Povečini je srčno popuščanje pri populaciji s povišanimi vrednostmi Lp (a) posledica miokardnega infarkta oz. ishemične bolezni srca ter degenerativne aortne stenoze. Kljub temu pa je polimorfizem rs3798220 povezan z višjo pojavnostjo srčnega popuščanja, ki ni posledica ishemične bolezni srca ali aortne

stenoze. V preglednem članku predstavljamo patofiziološki in klinični pomen hiperlipoproteinemije a pri ishemični bolezni srca, degenerativni aortni stenozi ter srčnem popuščanju, vključno z razpravljanjem.

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1 Introduction

Cardiovascular diseases, in particular ischaemic heart disease (IHD), degenerative aortic stenosis (DAS) and heart failure (HF), are significant causes of morbidity and mortality in the developed world (1-3). One of the most important risk and causative factors for IHD are elevated concentrations of LDL cholesterol (4,5). Elevated LDL concentrations are recognized as one of the main risk factors for the development of DAS (6). The relationship between increased LDL concentrations and DAS progression was first shown by a small retrospective study (7), which served as a basis for further randomized trials on the influence of lowering LDL on DAS progression. While lowering LDL is key to prevent the development and progression of atherosclerosis and thus significantly reducing IHD incidence (8), the hypolipaemic therapy with statins with or without ezetimibe fails to prevent DAS progression (9-11). Increased concentrations of LDL do not seem to affect the development of HF unless HF is the consequence of IHD or DAS. However, in patients with ischaemic HF, lowering LDL cholesterol with statins has not proven effective (12). The GISSI-HF study, which included patients with ischaemic and non-ischaemic HF, treated with polyunsaturated n-3 fatty acids, showed similar results (13). Increased LDL cholesterol concentrations are thus linked to the development of DAS and HF, especially as part of IHF, but its reduction, in particular with statins, does not halt the progression of DAS or HF . Therefore, we cannot conclude firmly that increased LDL concentrations have a causal relationship with DAS or HF. Among other lipid risk factors, lipoprotein(a) (Lp(a)) has been shown as an important risk factor for the development of IHD (14-16) and DAS progression (3,17). More data has come to light that Lp(a) is an independent risk factor for the development of HF, irrespective of IHD or DAS (18). It is interesting that not only Lp(a) concentrations, but a single nucleotide polymorphism (SNP), which determines increased Lp(a) concentrations, is related to development of HF. It has been shown that even at same Lp(a) concentration, the risk for the development of HF can be increased, depending on which SNP determines the Lp(a) concentration (18). The causal relationship between Lp(a) and development of DAS or HF has not been clearly established, but this relationship has clearly been established in the case of IHD, as lowering Lp(a) concentrations is at least partially responsible for reducing new IHD-related events and mortality (19-21).

The purpose of the article is to present and discuss the latest findings on the pathophysiological role of Lp(a) in the

development of IHD, DAS and HF. The most important studies on the role of Lp(a) with these diseases are shown in Table 1.

2 Lipoprotein(a)

Lipoprotein(a) was discovered more than 50 years ago and was recognized a decade later as a risk factor for coronary artery disease. Despite this observation, it has only gained importance in the last 10 years, when effective Lp(a)-lowering drugs appeared (22,23). Lp(a) consists of an LDL-like particle, in which apolipoprotein B (apoB) shares a single disulfide covalent bond with apolipoprotein A (apoA), the pathognomonic Lp(a) ingredient, similar to plasminogen (22,24) (Figure 1). Lp(a), especially because of its unique structure, participates in the pathophysiology of cardiovascular diseases with several unrelated mechanisms (25). Lp(a) has all the atherogenic characteristics of LDL cholesterol, including the affinity for oxidation after entering the vascular wall, creating the oxidized LDL cholesterol with immunogenic and inflammatory characteristics (26). However, Lp(a) is much more atherogenic than LDL in the same concentrations, because it also contains apo(a). Apo(a) is prothrombogenic due to various mechanisms, which include inflammation due to containing oxidized phospholipids (OxPL), the presence of lysine-binding sites, enabling accumulation in arterial walls, as well as through potential antifibrinolytic effects by inhibiting plasminogen activation (27). However, the majority of patients with elevated cardiovascular risk have normal Lp(a) concentrations and that there are significantly more patients with elevated LDL cholesterol than patients with elevated Lp(a) concentrations. Elevated concentrations of Lp(a) above 300 mg/L, which are already associated with increased cardiovascular risk, are present in 20–30% of patients (28,29).

Due to the complex molecular structure of Lp(a) and different apo(a) sizes, determining the concentration of Lp(a) is challenging. Several diagnostic tests (30), which are differently affected by apo(a) size (31), are available. Furthermore, the Lp(a) concentration, could be expressed in molar (nmol/L) or mass concentration (mg/dL). It has been shown that conversion between these two is far from accurate, dependining on apo(a) size and Lp(a) concentration (31-33). The latest recommendations of the British Cardiovascular Society suggest expressing Lp(a) concentration in nmol/L (32), measuring the Lp(a) concentration with appropriate antibodies, reducing the impact of apo(a) size. As Lp(a) concentration, expressed in mg/dL, encompasses the mass of apo(a), apoB100, cholesterol, cholesteryl esters, phospholipids and triglycerides. Because of the heterogeneity of apo(a) size, the standardization with one calibration method is still not possible (32). Due to the variable number of repetitive KIV_2 units in Lp(a) that act as multiple epitopes in immunoassays, it is important that the calibrators have the same number of apo(a) as the test samples. Otherwise, serum Lp(a) concentrations will be overestimated in those with a higher number of KIV_2 repeats and underestimated in those with a lower number. Even though some commercially available tests use traceable calibrators, this is not true for tests that express results as mg/dL (32).

The apo(a) coding gene (*LPA*) is located on the long arm of chromosome 6 (6q2,6-2,7) (34). Most variants of Lp(a) can be explained by genetic variability in *LPA*. So far, the most studied genetic variants have been the apo(a) polymorphisms, encoding the number of kringle IV type 2 (KIV_2) repeats. This accounts for

Table 1: A review of the most important studies on the association of ischaemic heart disease, degenerative aortic stenosis and heart failure with Lp(a) concentrations and polymorphisms in the *LPA* gene.

Disease	Study	Participants (n)	Duration of follow-up	Findings on the effect of Lp(a) concentrations	Findings on the influence of *LPA* polymorphisms	Ref.
Ischaemic heart disease	Copenhagen City Heart Study (CCHS)	Participants without clinically evident cardiovascular diseases (n = 9330)	10 years	**Odds ratio for MI** 50 – 290 mg/L 1.1 (95% CI 0.6 – 1.9) 300 – 840 mg/L 1.7 (95% CI 1.6 – 3.1) 850 – 1190 mg/L 2.6 (95% CI 1.2 – 5.9) > 1200 mg/L 3.6 (95% CI 1.7 – 7.7)	Not studied	(41)
	PROCARDIS	SNP discovery: patients with ischaemic heart disease (n = 3145) and controls (n = 3352) Confirmatory study: patients with ischaemic heart disease (n = 4846) and controls (n = 4594)	Cross-sectional study	Lp(a) concentration was associated with rs10455872 in rs3798220. together accounting for 40% of variability in Lp(a) concentrations.	rs10455872 odds ratio for coronary artery disease 1.70 (95% CI 1.49 – 1.95) rs3798220 odds ratio for coronary artery disease 1.92 (95% CI 1.48 – 2.49)	(16)
Degenerative aortic stenosis	Copenhagen City Heart Study (CCHS) Copenhagen General Population Study (CGPS)	Participants without clinically evident cardiovascular diseases (n = 10803) Participants without clinically evident cardiovascular diseases (n = 66877)	Up to 20 years	**Odds ratio for DAS** 50 – 190 mg/L 1.2 (95% CI 0.8 – 1.7) 200 – 640 mg/L 1.6 (95% CI 1.1 – 2.4) > 900 mg/L 2.9 (95% CI 1.8 – 4.9)	rs10455872 odds ratio for DAS 1.6 (95% CI 1.2 – 2.0) rs3798220 odds ratio for DAS 1.0 (95% CI 0.5 – 1.8)	(17)
	Cohorts for Heart and Aging Research in Genome Epidemiology (CHARGE)	Participants without clinically evident cardiovascular diseases from the MESA. FHS in AGES-RS studies (n = 6942)	Cross-sectional study	Statistically significant association between Lp(a) concentrations and rs10455872.	rs10455872 odds ratio for DAS 2.17 (95% CI 1.66 – 2.83)	(3)

Disease	Study	Participants (n)	Duration of follow-up	Findings on the effect of Lp(a) concentrations	Findings on the influence of *LPA* polymorphisms	Ref.
Heart failure	Copenhagen City Heart Study (CCHS) Copenhagen General Population Study (CGPS)	Participants without clinically evident cardiovascular diseases (n = 10855) Participants without clinically evident cardiovascular diseases (n = 87242)	Up to 21 years	**Odds ratio for HF. balanced for DAS and MI** 80 – 190 mg/L 1.09 (95% CI 0.97 – 1.34) 200 – 670 mg/L 1.14 (95% CI 0.97 – 1.34) 680 – 1530 mg/L 1.43 (95% CI 1.16 – 1.78) > 1530 mg/L 1.80 (95% CI 1.05 – 3.08)	Odds ratio for HF. balanced for DAS and MI rs10455872 1.12 (95% CI 1.01 – 1.23) rs3798220 1.50 (95% CI 1.23 – 1.82)	(18)
	Atherosclerosis Risk in Communities Study (ARIC)	Participants without clinically evident cardiovascular diseases (n = 14154)	Median 23.4 years	**Odds ratio for HF** 25.4 – 55.9 mg/L 1.05 (95% CI 0.92 – 1.20) 57.3 – 112.9 mg/L 1.09 (95% CI 0.96 – 1.25) 114.3 – 229.6 mg/L 1.21 (95% CI 1.06 – 1.38) 231.0 – 1082.3 mg/L 1.16 (95% CI 1.02–1.34) **Odds ratio for HF. balanced for MI** 25.4 – 55.9 mg/L 1.02 (95% CI 0.86 – 1.20) 57.3 – 112.9 mg/L 1.08 (95% CI 0.92 – 1.27) 114.3 – 229.6 mg/L 1.12 (95% CI 0.95 – 1.31) 231.0 – 1082.3 mg/L 1.07 (95% CI 0.91–1.27)	Not studied	(42)
	Multi-Ethnic Study of Atherosclerosis (MESA)	Participants without clinically evident cardiovascular diseases (n = 6809)	Median 13 years	**Odds ratio for HF** African Americans 1.00 (95% CI 0.80 – 1.26) White 1.20 (95% CI 1.036 – 1.40) Americans of Chinese descent 0.90 (95% CI 0.57 – 1.44) Latin Americans 0.94 (95% CI 0.77 – 1.13)	Not studied	(44)

Legend: CI – confidence interval, DAS – degenerative aortic stenosis, MI – myocardial infarction, HF – heart failure, Lp(a) – lipoprotein(a), Ref. – reference.

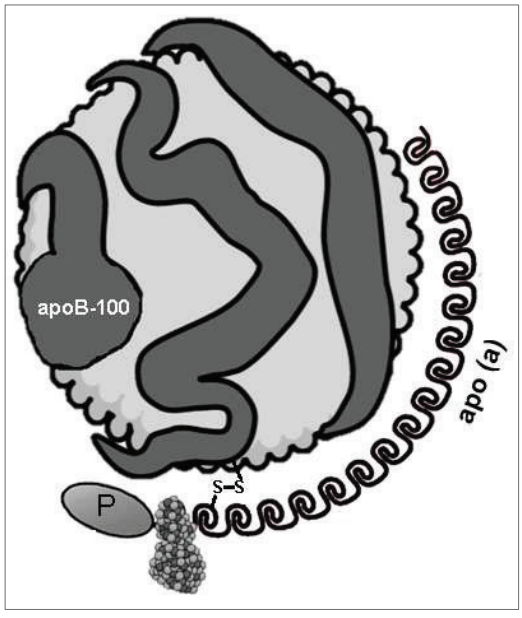

Figure 1: Lp (a) structure.
Lipoprotein(a) (Lp(a)) consists of an LDL-like particle, apolipoprotein B (apo(B)) and apolipoprotein(a) (apo(a)).

30–70% of Lp(a) variability in a population (Figures 1 and 2). There is an inverse correlation between apo (a) isoform size (i.e. KIV_2 repeats) and Lp(a) concentration (35). Elevated concentrations of Lp(a) and smaller apo(a) isoforms have a causal and independent relationship with coronary artery disease. Inside *LPA*, the KIV_2 copy number and presence of SNP polymorphisms, rs3798220 in rs10455872, are connected to increased Lp(a) concentrations and coronary artery disease rate (15,16,36).

The apo(a) size polymorphism is the main predictor of Lp(a) concentration, contributing 40–70% to Lp(a) concentration variability. It is by no means the only one, as other changes in the *LPA* gene contribute to concentration variability. In addition to genetic factors, systemic inflammation also affects Lp(a) concentrations. A systemic inflammatory response is involved in all stages of atherosclerosis. The apo(a) coding gene responds to inflammatory factors, such as interleukin 6. On the other hand, Lp(a) increases the release of proinflammatory cytokines. A race-dependent synergy between inflammation and Lp(a) expression has been presumed (37). Determination of genetic changes that have been shown to be associated with Lp(a) concentration should therefore be included for research purposes, as not all mechanisms that determine both Lp(a) concentration and its role in the atherosclerotic process are known. Perhaps, the findings of these studies will help us to better choose patients who would benefit the most from Lp(a)-lowering drugs, bringing us closer to personalized medicine. The concentration of Lp(a), which

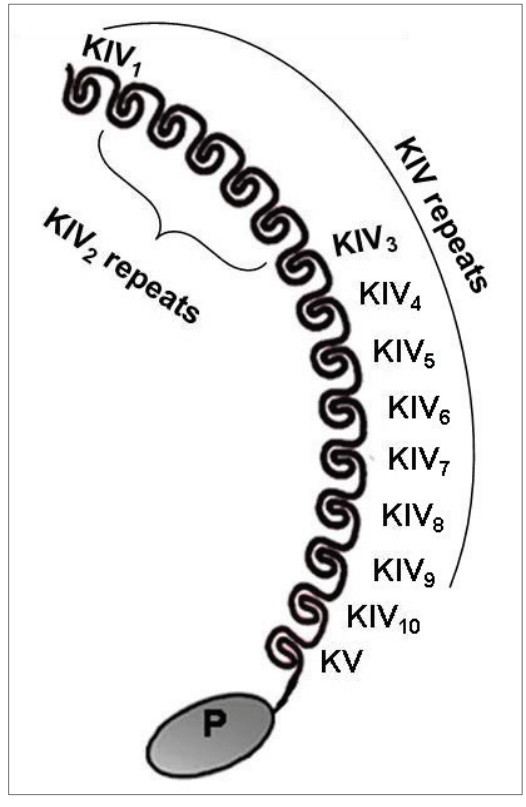

Figure 2: Apolipoprotein(a) molecular structure.
Apolipoprotein(a) (apo(a)) consists of 10 kringle repeats subtypes – one copy of KIV_1, multiple copies of KIV_2 and one copy of each repeat from KIV_3 to KIV_{10}, KV and an inactive protease-like P-domain.

varies up to 1,000 times between individuals, is hereditary and varies according to ethnicity (38-40). Elevations in serum Lp(a) concentrations are common, with 25% of the population having concentrations in the atherogenic range. Plasma Lp(a) concentrations and isoform size are determined by genetic variability in the apo(a) coding gene. Due to a lack of effective treatment, Lp(a) concentrations have never been routinely determined, only in target groups. We measured Lp(a) concentrations in patients with advanced atherosclerotic disease in the absence of risk factors, including LDL concentrations, in patients with familial hypercholesterolaemia, family history of IHD and increased Lp(a) concentrations, and in patients with early IHD (30). Based on the latest guidelines, we recommend determining Lp(a) concentrations at least once in life, and we are in particular still paying attention to the more vulnerable groups, for whom we determined the concentration of Lp(a) even before the new guidelines from 2019 were established (30).

The interracial differences in Lp(a) concentrations have been well studied; black individuals have 2–3x higher Lp(a) concentrations than white individuals (40) or Latin Americans (38). However, the 2–3x higher Lp(a) concentrations in black individuals do not correspond to a 2–3x higher IHD incidence (39). Cao et al. (38) have found that there is a statistically significant relationship between Lp(a) concentrations and aortic valve calcification in white individuals and marginally statistically significant in black individuals, while such a relationship was not found in Latin Americans and American of Chinese descent. In white subjects, the Lp(a) concentration of 300 mg/L was associated with higher incidence of aortic valve calcification, while in black subjects, only marginally more aortic valve calcification was seen at this Lp(a) concentration.

Several observational studies, including meta-analyses and genetic studies, pointed to a relationship between elevated Lp(a) concentrations and IHD, stroke and aortic valve stenosis (17,41,42). However, there are slightly fewer studies linking increased Lp(a) concentrations to an increased incidence of non-IHD or DAS-related HF (43-45).

3 Lipoprotein(a) and ischaemic heart disease

For a causal relationship between serum Lp(a) concentrations and disease, the most evidence exists for IHD (14,15,21,42,46). The only way to prove a causal relationship between lowering Lp(a) concentrations and a reduced incidence of coronary events would be to conduct a double-blind trials with a drug capable of exclusively lowering Lp(a) concentrations. Studies with PCSK9 inhibitors published to date have shown a reduction in the incidence of acute coronary events. However, it is not possible to separate the contribution of lowering LDL cholesterol from Lp(a) concentrations (21). On the other hand, Mendelian randomization studies, which use measurable changes in genes with known functions and whose purpose is to determine the causal effect of variable disease exposure in observational studies, can offer evidence for a causal relationship from allele frequencies with known risk in a population, independent of environmental factors (47,48). Mendelian randomization studies are based on cohort studies of disease in subjects with certain polymorphisms and comparing them to subjects without these polymorphisms – such randomization of alleles/polymorphisms at conception can be thought of as natural randomization.

To put it simply, the relationship between elevated Lp(a) concentrations and other genetic factors affecting the increase in Lp(a) concentrations with increased risk for myocardial infarction could hint at a causal relationship. The largest studies were conducted in Denmark, where a relationship between the incidence of IHD and Lp(a) concentrations and genetic factors, affecting Lp(a) concentrations, was evaluated in the Copenhagen City Heart Study (CCHS) and Copenhagen General Population Study (CGPS), with more than 12,000 subjects enrolled (49). During a median follow-up of 10 years, 1,142 participants (out of 9,330 healthy subjects) were diagnosed with IHD, including 498 with myocardial infarction (42). A stepwise increase in the incidence of IHD with increasing concentrations of Lp(a) was observed in both sexes. The risk was increased by 10% in women with Lp(a) concentrations between 50 to 290 mg/L (22nd to 66th percentile), 70% with concentrations between 300 to 840 mg/L (76th to 89th percentile), 160% with concentrations between 850 to 1,190 mg/L (90th to 95th percentile) and 260% with concentrations above 1200 mg/L compared to women with Lp(a) concentrations below 50 mg/L. In men, the risks were increased by 50%, 60%, 160% and 270%. Sex, smoking, diabetes, concentrations of total HDL and LDL cholesterol, apoB, and in women, menopause and the use of hormone replacement therapy all mildly increased the risk. In the same patient groups, the number of KIV_2 repeats was 6–99 and accounted for 21–27% of all Lp(a) concentration variability (15). In this population, the small number of KIV_2 repeats was associated with increased cardiovascular mortality, but not with non-cardiovascular mortality (49). The rs10455872 polymorphism in the *LPA* gene was linked to elevated Lp(a) concentrations and an increased number of KIV_2 repeats in homo- and heterozygotes (49). In their study, Clarke et al. (16) tested for associations with 48,742 SNPs in 2,100 candidate genes in more than 8,000 subjects, including patients with coronary artery disease and healthy controls. Two polymorphisms in the Lp(a) gene, rs10455872 and rs3798220, were found, accounting for 36% of total variability in Lp(a) concentrations. They are independent risk factors for coronary artery disease (70% and 90%, respectively).

In the Slovenian population, the relationship between IHD and Lp(a) concentrations has seldom been studied (50). In a cohort of 48 patients with familial hypercholesterolaemia, it was found that those with a history of myocardial infarction had marginally elevated Lp(a) concentrations, which could be attributed to the small sample size. At the same time, it is interesting that these patients had a statistically significant disrupted relationship between coagulation and fibrinolysis, which is one of the mechanisms by which Lp(a) increases the risk for acute coronary events (51).

4 Lipoprotein(a) and aortic stenosis

Degenerative aortic stenosis is the most common type of valvular heart disease in developed world (52). Aortic valve stenosis has long been considered only as a degenerative disease associated with the ageing of the valvular system. Since it has been definitively proven that it is linked to risk factors for atherosclerosis, such as smoking, arterial hypertension, diabetes and hyperlipidaemia (53,54). It should be noted that risk factors for the development of DAS may differ from factors influencing disease progression. The pathophysiology of DAS shows that the pathophysiological process at disease

onset is different from that which leads to progression (55).

Among the lipid factors, there is growing evidence that Lp(a) is also associated with DAS. The largest studies that assessed the relationship between Lp(a) concentrations and DAS (17) were conducted on the CCHS (56) and CGPS (57) population studies. There were 77,680 participants in both studies with a follow-up of 20 years. During this time, 454 participants were diagnosed with DAS. At the same Lp(a) concentrations as mentioned previously in connection with IHD, the risk for the development of DAS increased by 20%, 60%, 100% and 190%. Lp(a) concentrations were 110, 600 or 1,080 mg/L in heterozygotes or homozygotes without the rs10455872 polymorphism. With the rs798220 polymorphism, the concentrations were 140, 950 and 1,330 mg/L. Similarly, the Lp(a) concentrations increased with decreasing number of *LPA* KIV_2 repeats. The rs10455872 polymorphism accounted for 28%, rs798220 5% and the KIV_2 genotype 24% of the Lp(a) plasma concentration variability. Altogether, 41% of Lp(a) plasma concentration variability was accounted for.

A study with almost 7,000 participants (3) also confirmed, with computer tomography (CT) and clinical cases of DAS, that the rs10455872 polymorphism in the *LPA* gene and Lp(a) concentrations are both linked to aortic valve calcification. The sub-analysis of ASTRONOMER study, which consisted of 269 participants with mild or moderate DAS, also found an independent relationship between higher Lp(a) concentrations and a faster disease progression (58). Faster disease progression in patients with elevated Lp(a) concentrations was also mirrored in an increased need for aortic valve replacement.

The mechanism of Lp(a) action is probably very similar to its role in atherosclerosis by entering the arterial walls through the endothelium (15,16,59). Lp(a), caught in endothelial cells, is subject to oxidation, and oxidized Lp(a) plays the same role as oxidized LDL cholesterol in pathogenesis (25). In this way, Lp(a) contributes to the development of foam cells and inflammation due to its content of oxidized phospholipids. As such, the role of Lp(a) in the atherosclerotic process is a consequence of its pro-atherogenic activity – due to the similarity with LDL cholesterol – as well as its thrombogenic activity due to its similarity with plasminogen (60). As part of OxPL, oxidized LDL particles are involved in valvular system inflammation and calcification. Hypotheses about the role of Lp(a) in the progression of aortic stenosis was confirmed by a recent study, which found elevated metabolic activity and thus increased valvular calcification by using 18F-NaF PET/CT functional imaging, specific for evaluating calcification activity in patients with elevated Lp(a) concentrations (61). Mildly elevated metabolic activity in patients then correlated with echocardiographically determined disease progression and higher CT-evaluated calcium loads.

5 Lipoprotein(a) and heart failure

Heart failure affects 1–2% of adults in the developed world and up to 10% of the population above 70 years (2). In an ageing population, HF is an increasing cause of morbidity and mortality despite advances in clinical care (2). In approximately half of the patients, the cause of HF is IHD and its associated risk factors, with the other half attributed to patients with various cardiomyopathies and valvular diseases (62). In recent years, it has been found that Lp(a) is an independent prognostic factor for the development of HF, independent

of IHD or DAS (18,43,45). Kamstrup et al. (44) first discovered the relationship between elevated Lp(a) concentrations and elevated risk for HF. In the study with a follow-up of up to 21 years (median 7 years), 98,087 Danish participants were included, of which 4,112 were diagnosed with HF. They were tested for rs3798220 and rs10455872 polymorphisms in the *LPA* gene, which are linked to low numbers of KIV_2 repeats. The participants with genotypes at risk for these polymorphisms have elevated Lp(a) concentrations, which previous studies have shown is linked to an increased risk for myocardial infarction and aortic stenosis. In this study, it was demonstrated that 10-fold higher Lp(a) concentrations and *LPA* genotypes at risk for these two polymorphisms represented a 1.18 relative risk increase (95% CI: 1.04 to 1.34) for HF. They added that as much as 64% of this risk (95% CI: 45% to 99%) for HF manifested as myocardial infarction and DAS. In a multivariate analysis, elevated Lp(a) concentrations were found to be an independent prognostic factor for the development of HF. In those with Lp(a) concentrations from 80 to 190 mg/L, the risk was increased by 10% compared to participants with Lp(a) concentrations below 80 mg/L; by 24% in those with Lp(a) concentrations from 200 to 670 mg/L; by 57% in those with Lp(a) concentrations from 680 to 1,530 mg/L, and by 79% in those with Lp(a) concentrations above 1,520 mg/L (44). Of course, it was shown in this study, as in others (15,17,44), that increased Lp(a) concentrations are a prognostic factor for myocardial infarction and DAS as well. Considering the latter, the risk for developing HF was slightly reduced with these polymorphisms and with the previously mentioned Lp(a) concentrations was 9%, 14%, 43% and 80%. In the study, 46% of the variability of Lp(a) concentration was accounted for by the previously mentioned polymorphisms, rs3798220 and rs10455872, and the number of KIV_2 repeats. However, there are differences in the rate of HF predictive value according to the presence of the rs3798220 in rs10455872 polymorphisms. The risk is increased by 50% in the presence of only the first polymorphism, and in the presence of the second, taking into account the Lp(a) concentration, by only 12%. The rs3798220 polymorphism, present in only 3% of the general population, was significantly linked to the development of HF, which could not be accounted for by myocardial infarction or DAS. With rs10455872, present in 14% of the general population, almost all HF could be accounted for a past myocardial infarction or DAS. Given the racial differences in Lp(a) concentrations, these were also studied in relation to the development of HF. In the MESA study by Steffen et al. (45), 6,809 participants aged 45–84 years without known cardiovascular disease were included with a median follow-up of 13 years. During this time, 308 participants were diagnosed with HF. Only in white participants did increased Lp(a) concentrations prove to be an independent prognostic factor for higher risk of HF. White participants with Lp(a) concentrations above 300 mg/L had a 69% increased risk for the development of HF, and those with Lp(a) concentrations above 500 mg/L, the risk was 87% higher than in those with Lp(a) concentrations below 300 mg/L. Such a relationship could not be confirmed in black, Latin American or American participants of Chinese descent. In the ARIC study (43), 14,514 participants without clinically evident atherosclerosis were included with a median follow-up of 23.4 years. During this time, 2,605 participants were hospitalized due to HF. Lp(a) concentrations were directly associated with incident HF hospitalization

in models adjusted for age, race, gender, systolic blood pressure, history of hypertension, diabetes, smoking status, body mass index, heart rate, and HDL cholesterol with risk increasing by 24%. When a history of myocardial infarction was added to the model, the association was not statistically relevant anymore. The result was not at all surprising, considering that more than half of HF cases are caused by IHD and some by DAS. It is also interesting that the risk for the development of HF was nearly the same in the group with the highest Lp(a) concentrations as in the lowest concentration group, but the first group did include more patients with a history of myocardial infarction.

The mechanism of HF development in the absence of IHD or DAS has not been completely explained. Reduced perfusion at the microcirculation level is the most probable mechanism, as it has been shown to be reduced in patients with non-ischaemic HF (63,64). At the same time, lipoprotein apheresis was confirmed to improve perfusion in patients with IHD and elevated Lp(a) concentrations after only 24 hours (65). However, it should be noted that lipoprotein apheresis decreases fibrinogen and plasma viscosity as Lp(a) decreases, which could also contribute to perfusion improvement. Despite this, perfusion persists unchanged for the following 72 hours with normalization of the previously mentioned parameters, except for Lp(a) concentrations, so we can at least indirectly conclude that this is the cause of the improvement in perfusion. To date, there have been no studies investigating the effect of Lp(a)-lowering drugs on myocardial perfusion.

6 Conclusion

The adverse prognostic effects of Lp(a) and its role in cardiovascular disease have been known for several decades, but Lp(a) has only received increased attention with the development of new drugs in recent years (23). It is not yet clear if reducing Lp(a) on its own reduces the incidence of acute cardiovascular events; however, sub-analyses of two studies with PCSK9 inhibitors in patients after such an event showed that both alirocumab and evolocumab reduced the incidence of these events and reduced Lp(a) concentrations by approximately 25–40% (21,46). However, none of the sub-analyses tell us whether a decrease in Lp(a) has the effect of reducing the number of cardiovascular events by itself, as they were not conducted to prove that hypothesis and did not include exclusively patients with elevated Lp(a) concentrations. It should be noted that evolocumab and arilocumab both primarily lower LDL cholesterol concentrations by up to 60%, so it is not possible to know what proportion of reduced mortality comes from lower Lp(a) concentrations. Drugs that specifically lower Lp(a) by inhibiting the apo(a) RNA have proven to be effective in lowering Lp(a) concentrations (66). They promise much, but there are not enough studies on the effect of these drugs on lowering cardiovascular events available yet. Lp(a) has also been shown to be an independent risk factor in patients with DAS. The mechanism is probably similar as in atherosclerosis (38). To date, there have been no studies on the effect of Lp(a)-lowering drugs on DAS progression or reducing the need for surgery. Aortic stenosis is normally a disease of the elderly with multiple comorbidities and a higher risk for complications of surgery, which makes pharmacological interventions, including lowering Lp(a), a significant treatment breakthrough. The role of Lp(a) in HF pathogenesis has been the least studied and is not completely clear. It is known that more than a third of HF

cases cannot be linked to IHD or DAS, the most common causes of HF. It has been shown that only one of the two most common polymorphisms (18) contributing to significant Lp(a) concentration elevations is linked to higher HF incidence. With the growing recognition of the many roles of Lp(a) in the pathogenesis of various cardiovascular diseases, the recognition of clinical significance and the development of new drugs, Lp(a) is thus becoming an increasingly exciting and important field in cardiovascular medicine.

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