

The prevalence of increased lipoprotein (a) in the Czech general population and in patients with coronary heart disease

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Background. Lipoprotein(a) (Lp(a)) is a cardiovascular risk factor (RF) with potentially high clinical impact. However, in the “real world”, it remains largely overlooked, and the epidemiological circumstances of this RF have not yet been systematically studied in the Czech population. The aim of this study was to determine the prevalence of elevated values in cardiovascular patients and in the general population of this country.

Methods. A descriptive survey and case-control study were conducted on 2001 subjects [mean age 61.5 years ($\pm$ SD 12.5); 62.9% males], 1016 cases-patients with manifest coronary heart disease, (CHD), and 985 controls-a random general population sample.

Results. The CHD patients had a significantly higher prevalence of increased Lp(a) (≥ 125 nmol/L) than the control group (25.1 vs 12.9%, $P < 0.0001$). We found a similar relative difference using a lower cut-off, i.e., Lp(a) ≥ 105 nmol/L (28.9 vs. 14.6%, $P < 0.0001$). In case-control analysis, fully adjusted odds ratio for Lp(a) ≥ 125 nmol/L was 1.69 (95%CI: 1.13–2.53, $P = 0.011$), while for Lp(a) ≥ 105 nmol/L, 1.71 (95%CI: 1.16–2.52, $P = 0.006$). Increased Lp(a) was also independent of other conventional RFs, and the only major coincidence we found was elevated LDL cholesterol.

Conclusions. This study showed a significantly higher prevalence of Lp(a) in patients with manifest CHD compared to the general population. The systematic screening of this RF and pharmacologic intervention are probably warranted in routine clinical practice.

Key words: Lp(a), epidemiology, secondary prevention, primary prevention, EUROASPIRE, postMONICA

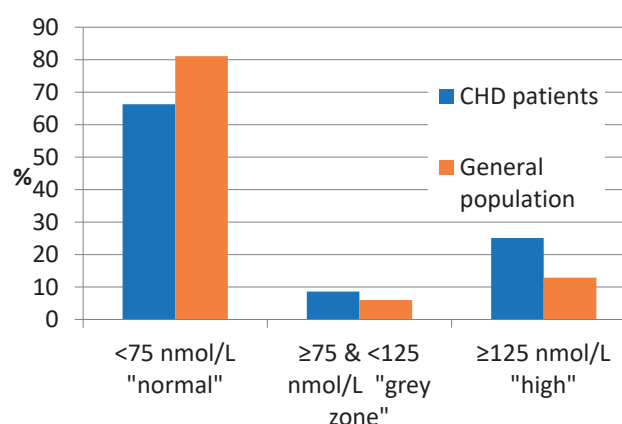
EPIDEMIOLOGY OF LIPOPROTEIN (A) IN CZECH POPULATION

Background: Lipoprotein(a) [Lp(a)] represents the cardiovascular risk factor with potentially high clinical impact. However, in “real world” it remains largely overlooked and the epidemiological circumstances of this risk factor were not yet systematically studied in Czech population.

Aims: To determine the prevalence of increased Lp(a) in cardiovascular patients and general population.

Methods: A descriptive survey and case-control study was realized on 1016 cases (patients with manifest coronary heart disease, CHD) and 985 controls (random general population sample).

Results: The CHD patients showed about two-fold higher prevalence of increased Lp(a) (≥ 125 nmol/L) than the control group (25.1 vs 12.9%, $P < 0.0001$). In case-control analysis, the adjusted odds ratio for Lp(a) ≥ 125 nmol/L was 1.69 (95%CI: 1.13–2.53, $P = 0.011$). Increased Lp(a) was also independent of other conventional risk factors, the only coincidence we found was elevated LDL cholesterol.



Increased Lp(a) showed high prevalence in Czech patients with manifest CHD. Because the targeted Lp(a) therapy is in the late stages of clinical research, it is appropriate to understand the epidemiological situation, before its implementation into clinical practice.

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INTRODUCTION

Lipoprotein(a) [lipoprotein “small a”; Lp(a)] was first described in 1963¹, and its potential importance in the etiology of atherosclerotic cardiovascular diseases (ASCVD) has been discussed since the late 1990s. It has not received much attention until at least 2010, and even then, the recommendations did not go beyond screening of this factor in people at particularly high cardiovascular risk². However, the last decade has produced convincing evidence of its important role in atherosclerosis and the risk of cardiovascular events. A subanalysis of the Copenhagen City Heart Study, involving 9330 participants without a history of ASCVD, found that the incidence of myocardial infarction increased linearly with increasing Lp(a) concentration. The risk of myocardial infarction reached statistical significance at approximately the highest tertile and was even 3.6 times higher from the 95th percentile onwards³. A meta-analysis of 7 studies, including more than 29 000 patients in secondary prevention, showed that Lp(a) concentration ≥ 50 mg/dL (≈ 125 nmol/L) was associated with an approximately 43% higher risk of major cardiovascular events and independently of LDL level and even in patients treated with statins (which is very important in context of secondary prevention of ASCVD!)⁴. Evidence of the causality of Lp(a) in the etiology of atherosclerosis and ASCVD has also been confirmed by Mendelian randomization studies with tens of thousands of participants^{3,5}.

The specificity of Lp(a) is not only its more complicated structure but also the fact that it is more than 90% genetically determined by variability in the gene for one of its key components (called apolipoprotein(a))^{6,7}. Many questions remain regarding the details of the pathophysiological proatherogenic mechanism. The accumulation of LDL-like particles in the atherosclerotic plaque likely does not play a significant role, and other proatherogenic mechanisms at the level of cell signaling are probably involved. So far, the most probable is the proinflammatory effect of Lp(a), increasing the size of the necrotic core of the plaque. There is also speculation about the role of this factor in the calcification process, especially in the valve area⁷. Essential for clinical practice is that the pharmaceutical industry has also responded unusually quickly, and we now have several different drugs to reduce Lp(a) under clinical development.

The formal determination of the “normal value” of Lp(a) remains highly controversial and is often questioned in risk factor (RF) analyses, which predominantly show a continuous relationship to the disease it causes, although it can be derived to some extent from epidemiological studies. It is also further complicated by the presence of at least two somewhat different determination methodologies. A consensus statement from 2022 recommends using the concept of a “gray zone” where the lower limit of confirmed Lp(a) hyperlipoproteinemia is considered to be values >50 mg/dL or 125 nmol/L, while the upper limit of excluded Lp(a) hyperlipoproteinemia is values <30 mg/dL or 75 nmol/L⁷. However, a very recent ESC/

EAS opinion from August 2025 adopted more stringent criteria: the “normal” values of Lp(a) were adjusted to ≤ 62 nmol/L, while the lower limit of high cardiovascular risk was set to ≥ 105 nmol/L (ref.⁸). As mentioned, the individual value of Lp(a) is largely genetically determined so that it can differ quite significantly between populations. Regarding the situation in the Czech population, objective, published data are nearly impossible to find or are only truly anecdotal. However, knowledge of the epidemiological situation is indispensable for screening for any RF and for formulating a potential treatment strategy. Similarly, in clinical practice, Lp(a) has remained mostly overlooked. According to our previous analysis among 43,681 patients hospitalized for cardiovascular events (myocardial infarction, coronary revascularization, valve replacement, stroke, or heart failure) between 2003 and 2023, only 8.2% had a determined Lp(a) concentration⁹. Even worse is probably the situation in the outpatient sphere.

Our analysis aimed to determine the distribution of Lp(a) in the Czech population, both in general “healthy” individuals and in patients with already manifest coronary heart disease (CHD).

METHODS

The independent institutional board (Ethics Committee of the University Hospital and Medical Faculty Pilsen) approved the study protocol. All procedures were conducted in accordance with the principles of Good Clinical Practice and the ethical standards outlined in the latest Declaration of Helsinki. Written informed consent was obtained from all participants included in the study at the baseline visit. The data were stored and evaluated in accordance with the provisions of the GDPR of the European Union.

Design and study population

The analysis represents a descriptive epidemiological survey and case-control analysis study, a secondary analysis conducted on existing samples from epidemiological surveys. The sampling process of both samples (cases and controls) was described in detail elsewhere.

The first sample (“cases”) represents patients with clinically manifest CHD, examined as part of the EUROASPIRE project¹⁰⁻¹². Patients aged less than 80 years and hospitalized with acute coronary syndrome and/or coronary revascularization were retrospectively identified from the hospital records. Recruitment of patients began with the most recent hospital record and proceeded backward until the required initial sample of 625 subjects in each of the three cohorts was selected, and responders (i.e., those who attended the clinical examination, $\approx 74\%$ of initial sample) were interviewed 6–24 months after the qualifying coronary event. For this analysis, we pooled three independent cohorts, i.e., EUROASPIRE III, IV, and V, examined in 2006–710, 2012–1311, and 2016/1712, respectively.

The second sample (“controls”) represents a random general population-based cohort examined in 2016/17 as a part (residents of Pilsen and vicinity) of the Czech post-MONICA project; all details are reported elsewhere again¹³. Initially, a random 1% sample of Pilsen region residents, aged 25–75 were selected from the General Health Insurance Registry¹⁴. Among responders, 632 individuals were originally examined in 2008 and then subsequently attended a follow-up examination in 2016/17. Additionally, an independent sample of 399 individuals was examined in 2017, using the same selection process and protocol. For this analysis, we combined these two independent cohorts into a single “controls” group.

Data collection

The details of the study protocol were reported elsewhere^{15,16}; in general, the same principles were applied to both samples (cases and controls). Briefly, all responders underwent an ad-hoc one-time examination. Information on each subject’s characteristics, personal and family history of coronary artery disease, lifestyle (smoking, drinking, exercise habits, etc.), and pharmacotherapy was obtained. Height and weight were measured using a SECA 767 (SECA GmbH & Co., Hamburg, Germany) scale with a telescopic measuring rod. Body mass index (BMI) was calculated as body weight (kg)/height²(m²). Blood pressure (BP) was measured using the auscultatory technique and an appropriately sized cuff. Three measurements were performed on the right arm in the sitting position, and average BP was used for analysis; mean arterial pressure (MAP) was calculated as one-third systolic pressure plus two-thirds of diastolic pressure. Waist circumference was measured using a metal tape applied horizontally at the point midway in the mid-axillary line between the lowest rim of the rib cage and the tip of the hip bone (superior iliac crest) with the patient standing. Breath carbon monoxide was measured using a SMOKERLYSER device (Model Micro+, Bedfont Scientific, Upchurch, UK) to verify smoking status (with 10 ppm of breath carbon monoxide as the cut-off point).

Venous blood samples were drawn after patients had fasted for at least 12 h. All laboratory examinations were performed in series from aliquots stored at –80 °C. Essential laboratory examinations (glycemia, serum lipids, creatinine) were done as a part of the routine clinical management in the central hospital laboratory (Department of Clinical Biochemistry and Hematology, University Hospital Pilsen; only standard commercial kits and analytical platforms were used, namely COBAS 8000 analytical platform, ROCHE Diagnostics, Basel, Switzerland). HbA_{1c} was determined from whole blood by ionex liquid chromatography using a G7 analyzer (TOSOH, Tokyo, Japan). LDL cholesterol was calculated using the Friedewald equation, i.e., LDL = total cholesterol – HDL – (TG/2.2), while estimated glomerular filtration rate (eGFR) was calculated by individual creatinine values using the CKD-EPI formula¹⁷.

The individual Lp(a) concentrations were quantified in series from EDTA-plasma aliquots stored at –80 °C.

We used a commercial particle-enhanced immunoturbidimetric assay (Tina-quant Lipoprotein(a) Gen.2, ROCHE Diagnostics) on the COBAS COBAS c701 analytical platform.

Data management

The original sample of “cases” consisted of 1387 subjects, but 371 patients had to be excluded due to unavailable aliquots or other technical problems (highly lipemic plasma, insufficient volume...). For the same reasons, we excluded 46 subjects from the “control” group.

Individual Lp(a) concentrations were dichotomized according to the 2022 consensus⁷ into three strata: <75, 75–124.9, and ≥125 nmol/L. Secondary analysis was also conducted using updated strata based on the new consensus from 2025 (ref.⁸): ≤62, 62.1–104.9, and ≥105 nmol/L.

If Lp(a) was treated as a continuous variable (for example, in linear regression), we performed a logarithmic transformation due to the highly nonparametric distribution. Current smoking was defined as self-reported or, in the case of more than 10 ppm of breath carbon monoxide as measured by the Smokelyser device. Raised blood pressure (BP) was defined as systolic blood pressure ≥140 mmHg and/or diastolic BP ≥90 mmHg. Overt diabetes was defined as fasting glucose ≥7.0 mmol/L and/or the use of anti-diabetic medication. Other conventional RF were dichotomized into binary variables with limits based on the 6th European Guidelines for Cardiovascular Prevention¹⁷. The eGFR values were dichotomized according to the National Kidney Foundation’s Kidney Disease Outcomes Quality Initiative¹⁸. Additionally, “history of ASCVD” was defined as any self-reported or documented major cardiovascular event/condition (myocardial infarction, stroke, peripheral vascular disease, ...), including any revascularization procedures in the group of “controls” (general population), while in the “cases”, all subjects are automatically positive for this factor.

Statistical analyses were performed using STATISTICA 14 (TIBCO Software Inc, Palo Alto, CA, USA) and STATA 8 (STATA Corp LP, College Station, TX, USA).

The first part of the analysis represents a descriptive survey comparing the prevalence of the increased Lp(a) (categorized by different cut-off points) among patients with clinically manifest CHD (cases) and the general population (controls), and χ^2 test were used for comparison. Moreover, we compared the relative risk of having increased Lp(a) between manifest CHD and the general population by Poisson regression with robust variance (adjusted for age decade and male gender). The second part represents a case-control analysis of increased Lp(a) and other conventional RF or treatments as confounders; multiple logistic regression was applied and we used manifest CHD as the dependent variable. Finally, we tested the independence of Lp(a) from conventional RF or treatments, and we used multiple linear or logistic regression, with log-transformed Lp(a) concentration or Lp(a) ≥125 nmol/L as dependent variable, respectively.

RESULTS

The total study population consisted of 2001 subjects (mean age 61.5 years ($\pm$ SD 12.5); 62.9% males); 1016 cases (patients with manifest coronary heart disease) and 985 cases (random general population sample) – the baseline characteristics of the two groups are listed in Table 1. CHD subjects were significantly older and consisted proportionally of many more males than females, and unsurprisingly, differed in several other ways from general population-based controls (Table 1). In the same way, mean Lp(a) was $\approx$ 50% higher in cases than in controls.

The distribution curves of Lp(a) in cases and controls are shown in Fig. 1. The parameter showed a highly nonparametric distribution, skewed to the right (higher Lp(a) concentrations) in both groups, and was differently distributed in patients with CHD compared to the general population. Median of Lp(a) in CHD patients was 26.2 (IQR: 8.5–125.5) nmol/L, while in the general population it was 13.7 (IQR: 6–44.3) nmol/L. The proportion of all three categories of Lp(a) concentration is shown in Table 1. The group of CHD patients showed about a two-fold higher prevalence of increased Lp(a) ($\geq$ 125 nmol/L) than the general population (25.1 vs 12.9%, P by χ^2 test

Table 1. Baseline characteristics of study samples [mean (standard deviation) or factor proportion].

	CHD patients “cases”	General population “controls”	P
n	1016	985	–
age [years]	65.3 (8.97)	57.6 (14.2)	<0.0001
gender [n (%) of males]	793 (78.1)	466 (47.3)	<0.0001
history of vascular disease [§] [%]	1016 (100)	91 (9.2)	<0.0001
current smoking [n (%)]	189 (18.6)	197 (20.0)	0.593
body mass index [kg/m ²]	29.7 (4.72)	28.1 (5.05)	<0.0001
body mass index $\geq$ 30 kg/m ² [n (%)]	435 (42.9)	305 (31.0)	<0.0001
waist circumference [cm]	104.7 (12.5)	97.2	<0.0001
increased waist circumference [†] [n (%)]	682 (67.2)	548 (55.7)	<0.0001
systolic blood pressure [mmHg]	135.2 (17.6)	131.8 (17.3)	<0.0001
diastolic blood pressure [mmHg]	83.0 (10.4)	81.2 (10.0)	<0.0001
raised blood pressure [‡] [n (%)]	454 (44.7)	365 (37.1)	<0.0001
total cholesterol [mmol/L]	4.35 (1.21)	5.18 (1.00)	<0.0001
HDL-cholesterol [mmol/L]	1.25 (0.34)	1.57 (0.42)	<0.0001
LDL-cholesterol [mmol/L]	2.29 (0.92)	3.02 (0.91)	<0.0001
triglycerides [mmol/L]	1.82 (1.59)	1.31 (0.71)	<0.0001
LDL $\geq$ 1.8 mmol/L [n (%)]	669 (68.0)	915 (93.3)	<0.0001
triglycerides $\geq$ 1.7 mmol/L [n (%)]	414 (40.9)	215 (21.8)	<0.0001
fasting glycemia [mmol/L]	6.89 (2.96)	5.46 (1.03)	<0.0001
HbA1c [mmol/mol]	46.4 (16.5)	37.7 (6.7)	<0.0001
overt diabetes [#] [n (%)]	425 (41.8)	95 (9.6)	<0.0001
estimated glomerular filtration* [mL/min]	67.7 (22.9)	87.2 (18.2)	<0.0001
estimated glomerular filtration* $<$ 60 mL/min [n (%)]	349 (38.3)	69 (7.4)	<0.0001
any antihypertensives [n (%)]	988 (97.2)	373 (37.9)	<0.0001
betablockers [n (%)]	867 (85.3)	144 (14.6)	<0.0001
RAS blockers [n (%)]	813 (80.0)	201 (20.4)	<0.0001
statins [n (%)]	920 (90.6)	192 (19.5)	<0.0001
antidiabetics [n (%)]	276 (27.2)	79 (8.2)	<0.0001
Lp(a) [nmol/L] – mean (SD)	72.4 (87.1)	44.6 (65.9)	<0.0001
– median (interquartile range)	25.2 (8.5–125.5)	13.7 (6.0–44.3)	
Lp(a) $<$ 75 nmol/L [n (%)] ^a	674 (66.3)	799 (81.1)	<0.0001
Lp(a) $\geq$ 75 & $<$ 125 nmol/L [n (%)] ^a	87 (8.6)	59 (6.0)	
Lp(a) $\geq$ 125 nmol/L [n (%)] ^a	255 (25.1)	127 (12.9)	
Lp(a) $\leq$ 62 nmol/L [n (%)] ^b	647 (63.7)	775 (78.7)	<0.0001
Lp(a) $>$ 62 & $<$ 105 nmol/L [n (%)] ^b	75 (7.4)	66 (6.7)	
Lp(a) $\geq$ 105 nmol/L [n (%)] ^b	294 (28.9)	144 (14.6)	

P value by Mann-Whitney U test (continuous variables) or χ^2 test (categorized variables);

[§]history of myocardial infarction or any other vascular disease, incl. revascularizations; [†]waist circumference $\geq$ 102 cm (males) or $\geq$ 88 cm (females);

[‡]systolic blood pressure $\geq$ 140 mmHg and/or diastolic blood pressure $\geq$ 90 mmHg; [#]highest fasting glucose $\geq$ 7 mmol/L, history of diabetes and/or treatment with antidiabetics; *by CKD-EPI standard;

^astratification by Expert Consensus from 2022 (ref. ⁷); ^bstratification by Expert Consensus from 2025 (ref. ⁸);

<0.0001). Additionally, we compared the prevalence of subjects with a lower cut-off Lp(a) ≥ 105 nmol/L (Table 1), and observed nearly identical relative differences between the groups (28.6 vs. 14.6%, $P < 0.0001$). The age and gender adjusted risk ratio (by Poisson regression) for having Lp(a) ≥ 125 nmol/L was 2.00 (95%CI's: 1.62–2.47, $P < 0.0001$; CHD patients *versus* general population), while the risk ratio of having Lp(a) ≥ 105 nmol/L was 2.03 (95%CI's: 1.68–2.47, $P < 0.0001$).

The case-control analysis was done in two ways. The first analysis compared all cases and controls, and the odds ratio for Lp(a) ≥ 125 nmol/L was 1.69 (95%CI: 1.13–2.53, $P = 0.011$), while for Lp(a) ≥ 105 nmol/L, 1.71 (95%CI: 1.16–2.52, $P = 0.006$). Second case-control analysis was performed with all cases, but we excluded 91 subjects with a history of ASCVD from controls; odds ratio for Lp(a) ≥ 125 nmol/L was 1.60 (95%CI: 1.02–2.51, $P = 0.042$), while for Lp(a) ≥ 105 nmol/L 1.71 (95%CI: 1.10–2.65, $P = 0.016$). (all four models were adjusted for all other RF or treatments, similar to those mentioned in Table 2b).

Finally, in the full sample (CHD patients *plus* the general population), we tested the independence of Lp(a) from conventional RF or treatments. In the continuous model (Table 2a), LDL, treatment with statins, and a history of vascular disease showed a positive association. In contrast, gender and triglycerides showed a negative association with Lp(a) as the continuous dependent variable. In a categorized manner (Table 2b), history of ASCVD, LDL ≥ 1.8 mmol/L and statin treatment was positively associated with the step-wise regression model, while gender was negatively associated.

In this pooled sample we also compared the Lp(a) status by gender. Males showed slightly lower median Lp(a) concentration than females (17.3 *versus* 21.2 nmol/L, respectively; $P = 0.535$ by Mann-Whitney U test) as well as marginally lower prevalence of Lp(a) ≥ 125 nmol/L (17.8 *versus* 18.5%, respectively; $P = 0.071$ by χ^2 test).

DISCUSSION

In the present study, we confirmed the prevalence of elevated Lp(a) concentrations in the Czech population and the general distribution of this potentially highly important cardiovascular factor. In contrast to previous, somewhat anecdotal evidence (at least for the Czech population), our data are based on well-defined samples from epidemiological studies, specifically for the general population (mostly primary prevention) and patients with already diagnosed coronary heart disease (secondary prevention).

The prevalence of increased Lp(a) (≥ 125 nmol/L) in our sample from the general population (“controls”) was $\approx 13\%$, while $\approx 15\%$ using the updated criterion (≥ 105 nmol/L). It was difficult to find data with which we could compare this result. There are at least two quite different methods of estimating Lp(a), and even using the same methods, studies often do not use the same cut-off points.

Since individual Lp(a) concentrations are largely genetically determined, significant differences between populations can reasonably be expected. In the available studies, the prevalence of hyperlipoproteinemia Lp(a), defined as ≥ 125 nmol/L or ≥ 50 mg/dL, has ranged from 7% to 26%, and such a wide range is probably due primarily to different methods of selecting the study sample (hospital-based sample vs. random population sample). The UK Biobank cohort, which includes more than 357,000 participants without manifest ASCVD, is probably the most similar to our series in terms of sampling methodology¹⁹. The prevalence of subjects with Lp(a) ≥ 125 nmol/L in this extensive population survey was 11.1%, which is relatively close to our results (despite the distance between the two populations). Indeed, it is questionable whether systematic screening of any RF makes sense given its relatively low prevalence. The current consensus to measure Lp(a) once in a lifetime (with the negligible direct costs of determining Lp(a), ie, less than 10 euros), seems to be a rational compromise⁷. However, information regarding the individual Lp(a) status of a particular person must not get “lost” somewhere in their medical documentation. In contrast, if an increased value of Lp(a) is found, the particular person should be viewed as the subject of significantly increased cardiovascular risk and adequately managed. Recent Guidelines from 2025 (ref.⁸) recommend that patients with high Lp(a) levels be strongly encouraged to take, or continue taking, high-intensity statins if their risk is sufficiently high, and a rigorous control of other conventional RF is undoubtedly indicated here. On the other hand, it is hardly expected that a person in primary prevention with elevated Lp(a) will be treated with one of the new drugs currently being under development (if only for economic reasons) in the coming years, except for extremely elevated values.

The epidemiological situation found in patients with manifest CHD (secondary prevention) was fundamentally different in our analysis. The prevalence of Lp(a) ≥ 125 nmol/L in these subjects was about twice as high as in those who had not yet experienced a cardiovascular event, and a more than two-fold higher prevalence risk remained after adjustment for conventional RF. For comparison, in a geographically relatively close German population, the prevalence of Lp(a) ≥ 50 mg/dL (≈ 125 nmol/L) in an extensive study of almost 53,000 subjects involved for any reason in the cardiovascular centre of the hospital was about 18.4% (ref.²⁰). This value is somewhat lower than that observed in our sample ($\approx 25.1\%$). In theory, this may be caused by different selection methods. Our sample of “cases” consisted exclusively of patients after myocardial infarction or angiographically proven and significant atherosclerotic disease of the coronary arteries, while the compared one²⁰ included all patients examined in the hospital (probably including those in whom a cardiovascular event was not confirmed). On the other hand, in our previous above-mentioned analysis on patients hospitalized for cardiovascular events, we found a prevalence of increased Lp(a) of more than 24% (≥ 125 nmol/L), i.e., nearly similar to the present, better defined sample⁹. Therefore, we

Table 2a. Predictors of lipoprotein(a) concentration in continuous manner (model A) in the full sample (cases *plus* controls).

	Full model (n=1954 [§])		Step-wise model (n=1965 [§])	
	β coefficient (95% confidence intervals)	<i>P</i>	β coefficient (95% confidence intervals)	<i>P</i>
<i>const.</i>	110.543 (77.244 – 143.843)	<0.0001	104.561 (94.408 – 114.715)	<0.0001
age	0.128 (–0.124 – 0.380)	0.318	–	–
male gender	–9.512 (–15.377 – –3.649)	0.001	–9.730 (–14.970 – –4.490)	<0.0001
history of vascular disease	13.783 (6.000 – 21.566)	0.001	15.709 (8.757– 22.660)	<0.0001
current smoking	–5.400 (–11.605 – 0.805)	0.088		
body mass index	–0.490 (–1.388 – 0.407)	0.284		
waist circumference	–0.001 (–0.356 – 0.355)	0.999		
mean arterial pressure	0.428 (–0.179 – 0.265)	0.705		
LDL-cholesterol	10.177 (7.344 – 13.011)	<0.0001	10.320 (7.549 – 13.089)	<0.0001
triglycerides	–4.886 (–8.442 – –1.328)	0.007	–5.834 (–9.153 – –2.514)	0.001
HbA1c	–0.031 (–0.246 – 0.184)	0.778		
estimated glomerular filtration	–0.029 (–0.160 – 0.103)	0.668		
any antihypertensives	0.867 (–6.808 – 8.542)	0.825		
statins	26.841 (19.468 – 34.213)	<0.0001		
antidiabetics	0.178 (–7.106 – 7.462)	0.962	27.064 (19.946 – 34.183)	<0.0001

Multiple linear regression, log-transformed Lp(a) as dependent (continuous) variable; [§]the final model was fitted using the maximum number of available observations.

Table 2b. Predictors of increased lipoprotein(a) concentration in categorized manner in the full sample (cases *plus* controls).

	Full model (n=1957 [§])		Step-wise model (n=1964 [§])	
	Odds ratio (95% confidence intervals)	<i>P</i>	Odds ratio (95% confidence intervals)	<i>P</i>
age decade	1.08 (0.96–1.21)	0.201		
male gender	0.60 (0.46–0.78)	<0.0001	0.61 (0.47–0.78)	<0.0001
history of vascular disease	1.52 (1.04–2.23)	0.031	1.46 (1.04–2.04)	0.030
current smoking	0.82 (0.60–1.12)	0.209		
body mass index ≥ 30 kg/m ²	1.00 (0.74–1.33)	0.973		
increased waist circumference	0.87 (0.64–1.17)	0.341		
raised blood pressure	1.08 (0.85–1.38)	0.534		
LDL ≥ 1.8 mmol/L	1.91 (1.39–2.62)	<0.0001	1.91 (1.40–2.62)	<0.0001
triglycerides ≥ 1.7 mol/L	1.06 (0.82–1.38)	0.649		
overt diabetes	0.97 (0.74–1.29)	0.856		
estimated glomerular filtration <60 mL/min	1.00 (0.74–1.35)	0.992		
brain natriuretic peptide ≥ 100 ng/mL	1.31 (0.97–1.78)	0.080		
treatments with antihypertensives	0.80 (0.53–1.20)	0.275		
treatments with statins	2.99 (2.08–4.31)	<0.0001	2.83 (2.01–3.99)	<0.0001

Multiple logistic regression, Lp(a) ≥ 125 nmol/L as dependent (categorized) variable; for definitions of variables *see* Methods or Table 1); [§]the final model was fitted using the maximum number of available observations.

cannot rule out that the Czech population (or at least the one around Pilsen) had a higher prevalence of elevated Lp(a) due to a slightly different genetic background.

In contrast to the majority of conventional RF, age is not a substantial cofactor of individual Lp(a) concentration, and this is also true in our series, even when cases and controls were tested separately. On the other hand, we observed a significant inverse association between Lp(a) and male gender (see Table 2); females showed marginally higher average concentration and prevalence of increased Lp(a). A similar phenomenon was also observed

in other series. In a meta-analysis of 36 prospective studies on more than 126,000 participants from 2009, females showed about 12% higher Lp(a) concentrations than males²¹. On the other hand, a recent registry-based study by Kaur and colleagues reported²² that risk conferred by elevated Lp(a) was similar between males and females.

From the point of view of clinical impact, the crucial question is what we can do for patients with ASCVD who are found to have elevated Lp(a). Unlike the situation a few years ago, we now have several different drug substances in the late phase of development, directly de-

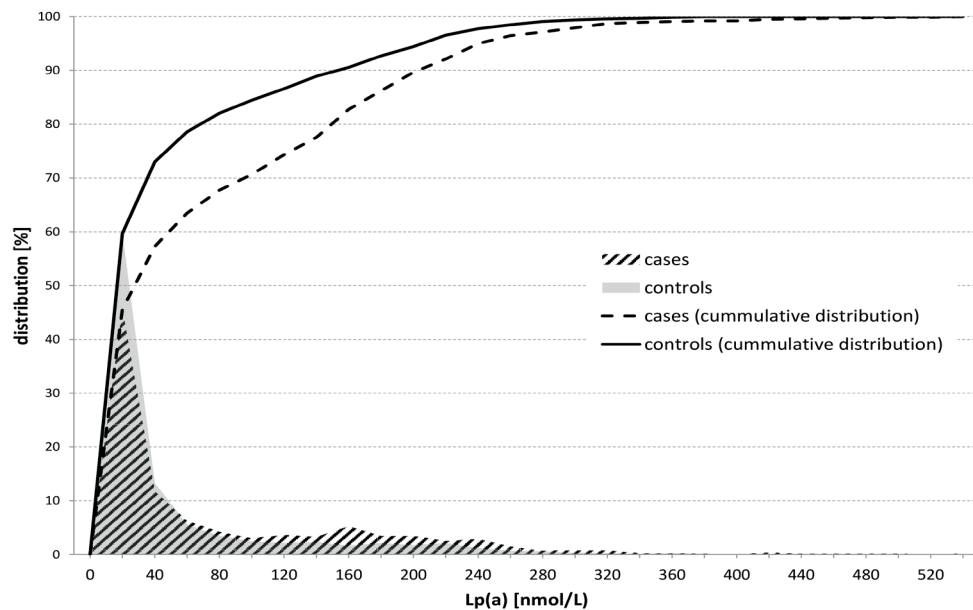


Fig. 1. Distribution (histogram and cumulative distribution curve) of lipoprotein (a) in patients with manifest coronary heart disease (*cases*) and the general population (*controls*).

signed to reduce this RF; most of them are based on a “modern” approach regulating Lp(a) levels at the level of gene expression. Olpasiran is a siRNA (small-interfering ribonucleic acid) targeting the synthesis of mature Lp(a) in the cytoplasm of hepatic cells. The phase II study (OCEAN(a)-DOSE) demonstrated that this drug, administered subcutaneously every 12 weeks, resulted in an almost 98% decrease in Lp(a) compared to placebo; almost all treated patients achieved levels of less than 125 nmol/L (ref.²³). The phase III study (OCEAN(a)-OUTCOMES) is also underway to confirm the risk reduction of recurrence of major cardiovascular events in patients with manifest CAD and Lp(a) levels of at least 200 nmol/L; results are expected by the end of 2026. Another drug being in an advanced stage of development is pelacarsen, an antisense oligonucleotide that targets the mRNA of the *LPA* gene. The phase II study with this drug again demonstrated a significant (about 72%) decrease in Lp(a) when administered once a month²⁴. The phase III study (Lp(a) HORIZON) in secondary prevention should already be completed, and the results are expected in 2026. Another two siRNA drugs (zerlasiran and lepodisiran) and even one oral drug (muvalaplin) are also under clinical testing.

It is reasonable to expect that if these phase III studies confirm the benefit of reducing Lp(a), a treatment strategy (indication criteria) for this RF in secondary prevention will be formulated on the basis (inclusion criteria) of these studies, while not on the (purely consensual) cut-off of increased Lp(a) (i.e. ≥ 125 nmol/L, or the updated one ≥ 105 nmol/L). Based on data from our epidemiological study, we can estimate how many patients in secondary prevention will be ultimately qualified for Lp(a) treatment. If treatment criteria are defined on the basis of the OCEAN(a)-OUTCOMES study (i.e., 200 nmol/L), only $\approx 10\%$ of patients in secondary prevention would meet them. If it is defined based on the Lp(a) HORIZON study (i.e., 175 nmol/L), the target group for secondary preven-

tion treatment would increase to $\approx 14\%$. In both cases, the overall population impact in reducing the risk of cardiovascular event recurrence would probably be quite limited (especially since it is difficult to expect that every patient who meets these criteria will ultimately receive the treatment). On the other hand, it is probably right to test a completely new treatment concept first on more severely affected individuals and, if its benefit is confirmed, to define the treatment criteria more liberally. It may also help in the future to better state the “normal value” of this RF (for example, in the case of LDL cholesterol, a similar process has been underway for more than 20 years, and maybe it's not even finished yet).

Of course, a pessimistic scenario also cannot be ruled out. Lp(a) can be considered a predictor (biomarker) of cardiovascular risk, but its therapeutic manipulation will not lead to any cardiovascular benefit (which would certainly not be the first case where otherwise “promising” treatment of an RF ultimately failed).

Study limitations

Our analysis has several limitations. From a purely epidemiological point of view, the study sample represents only the local population; controls are, by definition, inhabitants of Pilsen and its vicinity (the analysis was conducted at only one centre of an extensive epidemiological survey). Cases are patients clustered around large university-type hospitals with a large catchment area and are also to some extent a preselected sample, limited by the willingness to respond to the examination (among other things, the distance of their residence from the examination site). Therefore, any generalization must be made with some caution.

The case-control comparison is limited by the fact that the control group was a general population sample and, therefore, naturally included some individuals with already manifest ASCVD.

CONCLUSIONS

Elevated Lp(a) levels are likely to be an essential factor in individual cardiovascular risk, but have generally been overlooked in clinical practice. Its prevalence in our epidemiological survey in patients with manifest CHD is around 25%, in the general “healthy” population, it is about half. We already have a very effective targeted treatment available (although it is not yet ready for clinical use). The only thing we lack so far is evidence that therapeutic intervention for this factor will also lead to an improvement in the prognosis of the treated individuals (which we should have very soon). However, the high prevalence we confirmed in this study, along with its potential importance, already supports systematic screening for this factor.

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