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Lipoprotein apheresis in patients with peripheral artery disease and hyperlipoproteinemia(a)

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Abstract

Objective: Hyperlipoproteinemia(a) [Lp(a)-HLP] is a major risk factor for severe atherosclerosis. The present investigation sought to assess the effect of lipoprotein apheresis (LA) in patients with peripheral artery disease (PAD) and Lp(a)-HLP.
Methods: In January 2013, we started a registry for Lp(a)-HLP patients who receive weekly LA in our center. So far, ten patients with severe PAD and isolated Lp(a)-HLP who recently underwent revascularization (index procedure) have been included. Pain level, ankle-brachial-index (ABI), transcutaneous oxygen pressure ($tcpO_2$) and walking distance were determined before, as well as 1, 3, 6 and 12 months after initiation of LA. Furthermore, the mean time interval between revascularizations within the 12 months prior to the index procedure and up to 12 months after the index procedure was assessed.
Results: All analyzed parameters significantly improved under LA. When comparing the results before LA with the results after 12 months, the ankle-brachial-index increased from 0.5 ± 0.2 to 0.9 ± 0.1 ($P < 0.001$). The $tcpO_2$ levels also increased from 42.9 ± 2.3 mmHg to 59.0 ± 8.9 mmHg ($P < 0.001$). The improved microcirculation was associated with a reduction of the mean pain level from 7.0 ± 1.5 to 2.0 ± 0.8 ($P < 0.001$) as determined using the visual analog scale. The walking distance increased from 87 ± 60 m to 313 ± 145 m ($P < 0.001$). Importantly, the frequency of revascularization procedures was strongly decreased under LA. All patients combined underwent 35 revascularizations within the 12 months prior to the index procedure (mean interval between two revascularizations: 104.3 days). Since the index procedure, only one revascularization was necessary within 79 patient-months under LA (mean interval: 2404.5 days, $P < 0.001$).
Conclusion: LA improves circulation, oxygen supply, level of pain and walking distance in patients with severe PAD and Lp(a)-HLP. The frequency of revascularization procedures is strongly reduced under LA treatment.

Keywords: Hyperlipoproteinemia(a); Lipoprotein(a); Peripheral artery disease; Lipoprotein apheresis

1. Introduction

Hyperlipoproteinemia(a) [Lp(a)-HLP] has emerged as an independent risk factor for severe atherosclerosis [1−4]. Lipoprotein(a) [Lp(a)] is a plasma protein synthesized in the liver [5]. It consists of an LDL-like particle with one molecule of apolipoprotein(B100) and the specific apolipoprotein(a) [6,7]. The physiological role of Lp(a) is largely unknown. Lp(a) plasma concentrations are genetically determined [1]. The inter-individual plasma concentrations vary up to 1000-fold, ranging from 0.2 to >400 mg/dl [1]. Lp(a) acts pro-atherosclerotic and pro-thrombotic, thus leading to vessel occlusions via two different mechanisms [5]. The apolipoprotein(a) has a high

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structural homology to plasminogen and plasmin and competitively inhibits their binding and effect, resulting in reduced fibrinolysis [8]. Pro-atherosclerotic effects of Lp(a) are based on MAC-1-dependent recruitment of inflammatory cells, transport of oxidized phospholipids and stimulation of smooth muscle cell proliferation [9−11]. Clinical presentations of Lp(a)-HLP include coronary artery disease, cerebrovascular disease and peripheral artery disease (PAD) [12,13]. Currently, Lp(a) plasma levels from 30 to 50 mg/dl are defined as high risk and levels of >50 mg/dl as very high risk. The treatment goal is a Lp(a) level of less than 50 mg/dl [1]. However, the treatment options for Lp(a)-HLP are very limited. Plasma concentrations of Lp(a) are only slightly affected by diet and lifestyle and there is currently no drug for effective Lp(a) reduction available [1,14]. Today, the most effective therapy for Lp(a)-HLP is lipoprotein apheresis (LA), which has already shown great benefits in studies on coronary artery disease [14,15]. In Germany, LA is therefore recommended in patients with Lp(a) levels above 60 mg/dl and documented progression of cardiovascular disease [16,17].

In our clinic, we routinely treat patients with Lp(a)-HLP and severe PAD. These patients are often young and present with aggressive forms of PAD characterized by rapid progression despite optimal treatment, good compliance and adequate lifestyle. After revascularization treatment, these patients have a high rate of re-occlusions or in-stent restenosis. To expand the therapeutic options, we initiated a registry to analyze the effect of LA in patients with severe PAD and Lp(a)-HLP.

2. Methods

2.1. Study design

The present manuscript describes a prospective observational single center investigation. Patients were not randomized as they suffer from treatment resistant PAD and omission of LA seems not ethically justifiable (see discussion). Instead, we started an LA registry in January 2013 and have so far included 10 patients with severe PAD (stage IIb, III or IV) and isolated Lp(a)-HLP (LP(a) > 60 mg/dl), who recently underwent index revascularization (bypass, percutaneous transluminal angioplasty or stent implantation). The mean time interval between the index procedure and the first LA was 2.9 ± 0.6 days. We compared the clinical status of the patients before LA with the situation up to one year after the start of LA. Common risk factors were sufficiently treated and patients were compliant. However, these patients still suffered from rapid progression of PAD, including re-occlusion of bypasses and stents. After the index revascularization the following parameters were determined: ankle-brachial-index (ABI), walking distance, transcutaneous partial oxygen pressure ($tcpO_2$) and level of pain. Thereafter, LA was started as early as possible and performed once weekly. The follow up examinations were routinely scheduled after 1, 3, 6 and 12 months. Furthermore, the mean time interval between individual revascularization procedures (bypass surgery, percutaneous transluminal angioplasty [PTA] or stent implantation) within the 12 months prior and up to 12 months after the index procedure was assessed. The index procedure itself was not counted to prevent overestimation of the revascularization rate before LA. The present manuscript reports initial results from our registry. By the time of this analysis, 4 patients have completed 12 months follow up, 9 patients have completed 6 months follow up and all patients have completed 1 month follow up (79 patient-months). Baseline characteristics of the patients are presented in Table 1. All patients gave written informed consent.

2.2. Lipoprotein apheresis

Lipoprotein apheresis was performed with the "Life 18" apheresis unit from Miltenyi Biotec® (Bergisch Gladbach, Germany). Blood was continuously collected from a peripheral vein and anticoagulated. Plasma was then separated by filtration and transferred to the adsorber (TheraSorb®, Bergisch Gladbach, Germany). The adsorber works with sheep antibodies bound to an agarose-matrix. The antibodies bind human LDL, very low density lipoprotein (VLDL) and Lp(a). The unit consists of two adsorbers, which are loaded and regenerated alternately. The purified plasma is re-united with the cellular components and returned to the patient over a second venous line. The LA takes 3−4 h and is performed once weekly.

Table 1
Patient characteristics.

n	10
Female, n (%)	5 (50%)
Age, years	55 ± 8.0
Body mass index, kg/m^2	26.5 ± 4.2
Lp(a) plasma level, mg/dl	
Before first LA (n = 10)	156.1 ± 97.5
After 1 month (n = 10)	102.6 ± 17.2
After 3 months (n = 9)	87.6 ± 9.9
After 6 months (n = 9)	73.9 ± 10.0
After 12 months (n = 4)	68.3 ± 6.9
Mean Lp(a) level reduction per LA (%)	65.8 ± 5.9
Low density lipoprotein cholesterol, mg/dl	85.2 ± 32.1
Total cholesterol, mg/dl	165 ± 15.0
Triglycerides, mg/dl	156 ± 23.5
High density lipoprotein cholesterol, mg/dl	55 ± 4.5
HbA1c in patients with diabetes mellitus, %	5.8 ± 0.6
PAD, n (%)	10 (100%)
Critical limb ischemia, n (%) (before index revascularization)	4 (40%)
Coronary artery disease, n (%)	7 (70%)
History of myocardial infarction, n (%)	2 (20%)
End-stage renal failure, n (%)	1 (10%)
Diabetes mellitus, n (%)	1 (10%)
Former smokers, n (%)	10 (100%)

When appropriate, data are given as mean ± SD. The Lp(a) levels were measured before the next LA.

2.3. Lipoprotein(a) measurement

For determination of Lp(a) plasma levels the Tina-quant® Lipoprotein(a) assay from Roche® was used. This quantitative assay is based on latex particles coated with anti-Lp(a) antibodies. During incubation, Lp(a) molecules and coated latex particles agglutinate and form antigen–antibody complexes. The degree of turbidity caused by these aggregates is then turbidimetrically determined with a Cobas c® analyzer. It is proportional to the Lp(a) concentration in the sample.

2.4. Ankle-brachial-index and transcutaneous partial oxygen pressure ($tcpO_2$)

After 10 min in a lying position, blood pressure was taken non-invasively in both arms. Blood pressure in both feet was determined using a pencil Doppler probe at the posterior tibial artery and dorsalis pedis artery. The quotient of peripheral and central blood pressure is the ankle-brachial-index (normal value: 0.9–1.2; PAD < 0.9, severe PAD < 0.5, media sclerosis >1.2). Thereafter, $tcpO_2$ levels were determined in the same position. Electrodes attached to both forefeet continuously measured the $tcpO_2$. We used a TCM4® monitoring device by Radiometer® (Berlin, Germany).

2.5. Walking distance and level of pain

The walking distance was determined by standard treadmill testing with a fixed grade of 12% and a constant speed of 3.2 km/h. The test was continued until claudication stopped the patient. The pain level was assessed using the visual analog scale (VAS) reaching from VAS 0 – no pain to VAS 10 – worst pain. Patients were asked for their mean pain level during everyday physical activity. After index revascularization no patient had pain at rest.

2.6. Statistical analyses

Unless stated otherwise, data are presented as mean ± standard deviation (SD). Statistical significance was calculated using the Holm-Sidak method for one-way repeated-measures analysis of variance (ANOVA) (SigmaStat 3.0, SPSS, Inc.). An error probability of $P < 0.05$ was considered statistically significant. In the diagrams, box plots depict the median as well as the 25th and 75th percentile. Whiskers indicate the 90th and 10th percentiles, respectively. Statistical outliers are depicted by dots (SigmaPlot 8.0, SPSS, Inc.).

3. Results

LA was successfully conducted once weekly with no procedure related adverse events. The peak Lp(a) plasma levels were reduced from 156.1 ± 97.5 mg/dl before the first LA to 68.3 ± 6.9 mg/dl after 12 months of LA (n = 4). The mean percentage reduction of the Lp(a) levels per single LA procedure was 65.8 ± 5.9% (Table 1). Before the index revascularization, four patients had a critical limb ischemia (CLI), which was resolved prior to initiation of LA. The mean ABI before LA was 0.5 ± 0.2. Under treatment with LA, the ABI continuously increased and, with 0.9 ± 0.1, almost reached normal values after 12 months ($P < 0.001$, Fig. 1A). The mean $tcpO_2$ before start of LA was 42.9 ± 2.3 mmHg. After one month of treatment, the $tcpO_2$ already reached 50.1 ± 6.5 mmHg and finally climbed to 59.0 ± 8.9 mmHg after 12 months ($P < 0.001$, Fig. 1B).

Clinically, the patients suffered from a high mean pain level of 7.0 ± 1.5 at baseline with relevant impairment in quality of life. However, no patient had pain at rest after the index revascularization. The pain level improved rapidly and sustainably under treatment with LA. The mean pain level after 12 months was 2.0 ± 0.8 ($P < 0.001$, Fig. 1C). In good agreement with the improved perfusion (ABI) and oxygen supply ($tcpO_2$), the functional capacity, assessed by the walking distance, also increased under treatment. Starting with a mean walking distance of 87 ± 60 m at baseline, the mean walking distance after 12 months was 313 ± 145 m. Although there were variations between the patients, this represents an improvement of at least one PAD stage (on average, from IIb to IIa) ($P < 0.001$, Fig. 1D). Beside pain and impaired walking, major problems in these patients are recurrent occlusions of bypasses and stents requiring revascularization treatments (Fig. 2).

Importantly, the frequency of restenosis or reocclusions that necessitate reinterventions was strongly decreased under LA. The mean time interval between two revascularizations in the 12 months prior to the index procedure was 104.3 days (35 procedures in 120 patient-months). After the index procedure, so far only one revascularization was necessary, leading to a calculated mean time interval between two revascularizations of 2404.5 days (1 procedure in 79 patient-months, $P < 0.001$).

4. Discussion

The present data demonstrate that LA strongly reduces the number of revascularizations in patients with aggressive PAD and Lp(a)-HLP. LA significantly improves circulation and oxygen supply leading to a reduced pain level and an increased walking distance. First effects were already detectable after one month of LA and became continuously more pronounced over the first 12 months.

The fast improvement of circulation and oxygen supply under LA cannot only be explained by a reduction in the plaque-volume, which might occur at the earliest after 1–2 years of continuous treatment [18,27]. However, LA has several other effects that occur from the instance of treatment. These include reduction of the Lp(a) driven pro-

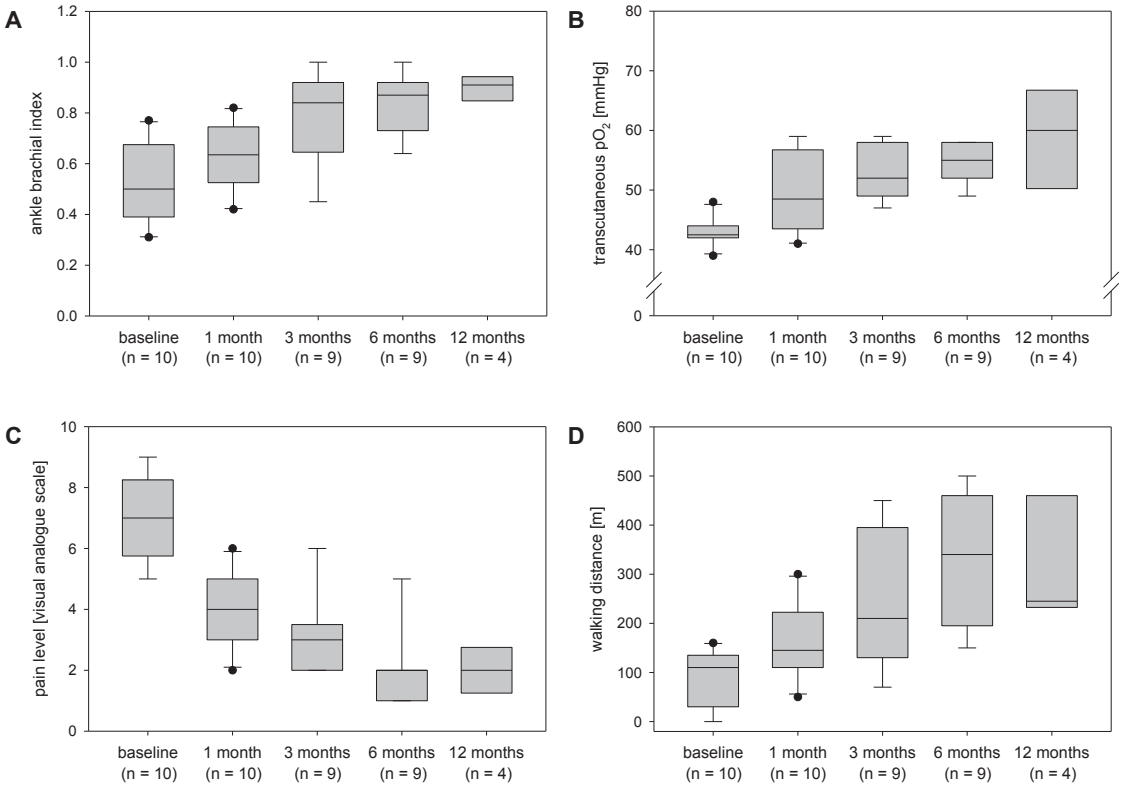

Fig. 1. Ankle-brachial-index (A), transcutaneous partial oxygen pressure ($tcpO_2$) (B), pain level (C), and walking distance (D) of the analyzed patients at baseline and under treatment with weekly LA. All parameters improved significantly under LA (Holm-Sidak method for repeated-measures ANOVA, $P < 0.001$; box plots depict the median as well as the 25th and 75th percentile. Whiskers indicate the 90th and 10th percentiles, respectively. Statistical outliers are depicted by dots).

coagulatory pattern, reduced susceptibility to LDL oxidation, reduction of inflammatory peptides and improved endothelial function [19–21]. This very complex pattern of LA effects leads to vascular tone reduction, reduced thrombogenesis, increased neo-angiogenesis and, importantly, to plaque-stabilization [19–21]. To what extent the lower Lp(a) levels after LA directly contribute to these effects is not known. All patients suffered from isolated Lp(a)-HLP, while all other risk factors were sufficiently treated. Therefore, the beneficial effect of LA supports the idea that Lp(a) is actually a causal factor for the treatment resistance and rapid progression of atherosclerosis. Recently, a study by Laschkolnig et al. described a significant association between elevated Lp(a) plasma levels, low-molecular-weight apo(a) phenotypes and PAD in three independent populations. The applied Mendelian Randomization approach also indicated a causal relationship between elevated Lp(a) and PAD [28].

Although it seems very unlikely that the observed improvements under LA would have occurred under optimal conventional treatment alone, only a randomized controlled trial could finally prove this hypothesis [14]. The main ethical problem of a randomized design is that a severely sick patient assigned as treatment-resistant might end up in the control group, where the only potentially helpful treatment is withhold. Previous data from non-randomized trials seem too good to justify such an approach [14,15].

Until now, there are no established medical alternatives for Lp(a) reduction. The only drug that significantly lowers Lp(a) levels is nicotinic acid, which can reduce plasma levels by approximately 25% [1,22]. However, treatment is often limited by severe side effects and the last available product Tredaptive® was withdrawn from the European market in 2013 [1]. Drugs with novel mechanisms are under development, including mipomersen, an apolipoprotein(b) synthesis inhibitor [23], cholesteryl ester transfer protein (CETP) inhibitors [24], PCSK9 inhibitory antibodies [25] and the interleukin-6 inhibitor tocilizumab [26]. CETP inhibitors and PCSK9 inhibitory antibodies have already shown their potential to significantly lower Lp(a) levels, however, their clinical effect is still under investigation.

To our knowledge, the present study is the first that analyzes the effect of LA in patients primarily affected by severe PAD and Lp(a)-HLP. Therefore, direct comparison with previous results is not possible. However, the large trials on LA in CAD patients with Lp(a)-HLP also observed a trend towards less PAD interventions under LA treatment [14,15].

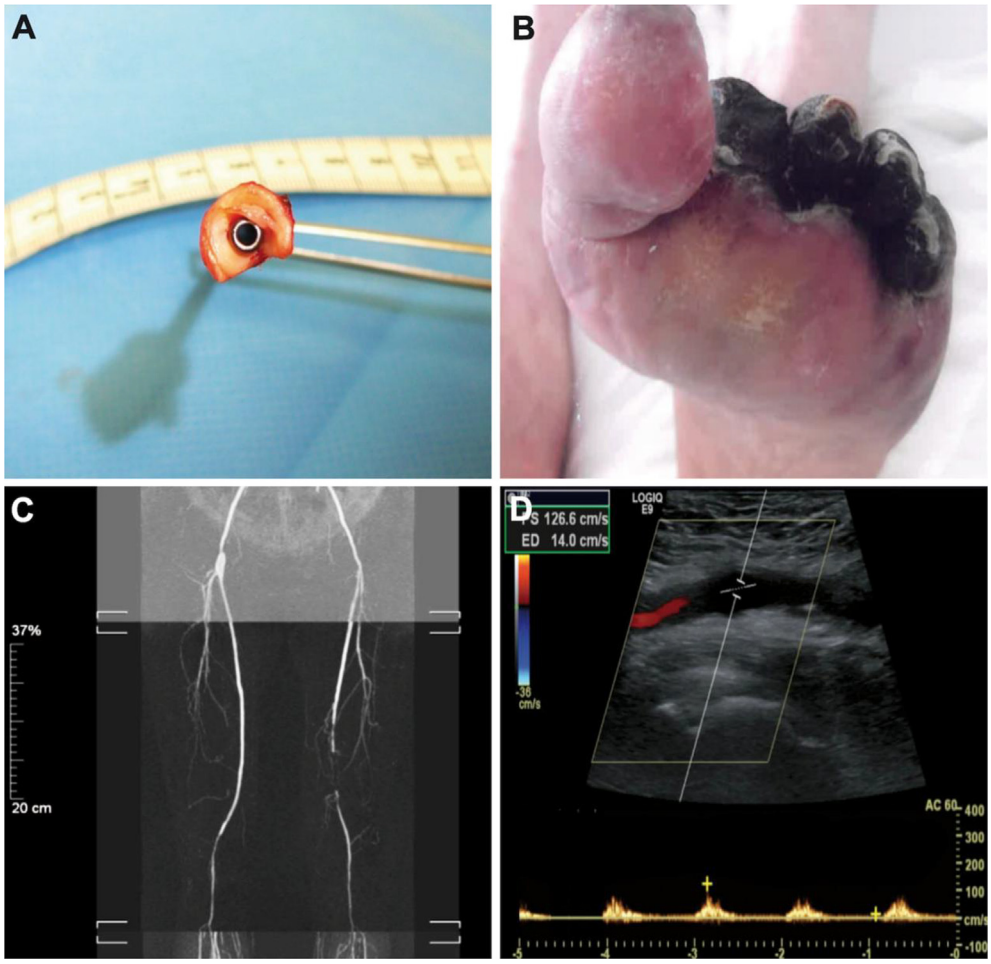

Fig. 2. A) Typical circular stenosis in a resection of the superficial femoral artery of a patient with severe Lp(a)-HLP. In contrast to plaques in patients with "common" atherosclerosis, the plaques in patients with Lp(a)-HLP often exhibit a circular shape, with no ulcerations, little or no calcification and a homogeneous internal structure. The circular stenoses range over long distances. (B) Clinical presentation of a patient with Lp(a)-HLP and PAD stage IV. (C) Typical MR-angiogram with a total occlusion of the left superficial femoral artery over a distance of 15 cm and the typical small lumen vessels. (D) In patients with Lp(a)-HLP duplex ultrasound typically exhibits thin lumen vessels without distinct plaques and only little echo contrast (example shows the right common femoral artery).

In our study, the mean Lp(a) level measured before start of LA was 156.1 ± 97.5 mg/dl, which is significantly above the levels reported in previous studies on Lp(a)-HLP and LA (Leebmann: 104.9 ± 45.7 mg/dl; Jaeger: 117.9 ± 42.0 mg/dl; Safarova: 105.0 ± 37.0 mg/dl) [14,15,29]. Obviously, our patients represent a very high-risk cohort, which might explain the high number of revascularizations prior to LA. Furthermore, we observed a stronger percental reduction of the mean Lp(a) levels during the first 12 months of LA (present study: 156.1 ± 97.5 mg/dl to 68.3 ± 6.9 mg/dl; compared to Jaeger: 117.9 ± 42.0 mg/dl to 75.1 ± 24.9 mg/dl; Leebmann: 104.9 ± 45.7 mg/dl to 86.8 ± 34.5 mg/dl; Safarova: 105.0 ± 37.0 mg/dl to 73.3 ± 22.3) [14,15,29]. This is mainly based on the higher baseline values. Interestingly, the Lp(a) levels achieved in the different studies after 12 months of LA are in a similar range. This might suggest that LA is able to reduce Lp(a) concentrations down to a comparable threshold level, which is not directly correlated to the baseline Lp(a) levels. As our patient cohort started with very high Lp(a) levels, this would explain the stronger percental Lp(a) reduction. Furthermore, the rebound velocity of the Lp(a) level after an LA procedure exhibits inter-individual differences. Therefore, our data on Lp(a) reduction may currently not be over-interpreted as the patient number is so far low, not all patients have completed 12 months follow up, and some patients in the cohort started with extremely high Lp(a) levels above 400 mg/dl but dropped extraordinarily strong (see high standard deviations at baseline). Therefore, the uncertainty factor is relevant and the currently very strong decrease in the mean Lp(a) levels might change in the course of the registry.

5. Limitations

The small number of patients is clearly a limitation of the present study. However, patient numbers in the field are

small and it would require multicenter trials or registries to analyze the effects in a larger scale. This investigation was designed as a pilot study, which now has to be followed by larger trials. A randomized controlled trial would surely be the better way to analyze the effects of LA, however as discussed above, so far it did not get ethical approval in Germany. The selection of patients that recently underwent successful revascularizations might introduce a selection bias, although we did not count the index procedure itself.

6. Conclusions

Patients with PAD and Lp(a)-HLP often suffer from uncontrollable progression of the disease. Diet, life style and available drugs have little effect. LA is currently the only way to significantly reduce Lp(a) plasma levels. The present study demonstrates that Lp(a) reduction via LA leads to strong symptomatic improvement and reduces the number of necessary revascularizations in these patients. Larger trials are needed to confirm these results and implement LA as standard therapy in patients with severe PAD and Lp(a)-HLP.

Conflict of interests

All authors declare that they have no conflicts of interest.

Sources of funding

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