Current Atherosclerosis Reports (2020) 22: 68
https://doi.org/10.1007/s11883-020-00886-0

NONSTATIN DRUGS (M. VRABLIK, SECTION EDITOR)

# Therapeutic Apheresis for Management of Lp(a) Hyperlipoproteinemia

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Published online: 18 September 2020


## Abstract

**Purpose of Review** High lipoprotein(a) (Lp(a)) level is an independent cardiovascular risk factor with higher prevalence among patients with atherosclerotic cardiovascular disease (ASCVD). The actual problem is that most currently available lipid-lowering drugs are unable to abolish Lp(a) pathogenicity. Lipoprotein apheresis (LA) is an effective method for elimination of atherogenic lipoproteins, but it is approved only in some countries for treatment of elevated Lp(a) level in the presence of progressive ASCVD. In recent years, new studies on LA were published and the purpose of this review is to present the information on optimal management of Lp(a) hyperlipoproteinemia by LA in the modern era.

**Recent Findings** Most clinical studies designed to treat Lp(a) hyperlipoproteinemia with different LA systems are small in size but demonstrate that the elimination of Lp(a) from bloodstream leads to reduction of inflammatory and prothrombotic process in a few months and to atherosclerotic plaques regression in 1.5 years. Treatment with LA for 2 to 5 years in terms of clinical trials and in real-world setting provides further evidence that Lp(a) reduction by 60–80% is associated with proportional decreasing of rate and risk of cardiovascular events.

**Summary** Specific Lp(a) apheresis is the only possible method that solely targets Lp(a). In most countries, non-specific LA is used for treatment Lp(a) hyperlipoproteinemia in very high-risk subjects with progressive ASCVD. PCSK9 inhibitors have only modest effect on significantly elevated Lp(a), whereas large population-based studies requested sustained and prolonged reduction of Lp(a) levels by 50–100 mg/dL to gain proportional decreasing of major adverse cardiovascular events.

**Keywords** Lipoprotein(a) · Specific Lp(a) apheresis · Lipoprotein apheresis · Atherosclerosis · Cardiovascular events

## Introduction

Elevated lipoprotein(a) (Lp(a)) is recognized as an independent cardiovascular risk factor with prevalence of about 20% in general population and much higher prevalence among subjects with atherosclerotic cardiovascular disease (ASCVD) [1••]. The latest European guidelines on dyslipidemia emphasize that Lp(a) level should be measured in each adult at least once to assess the lifetime risk of ASCVD development, and in persons at highest Lp(a) concentrations, the cardiovascular risk is equivalent to that in heterozygous familial hypercholesterolemia (FH) patients [2]. Owing to its unique structure, Lp(a) possesses atherogenic, prothrombotic, and pro-inflammatory properties that were proven in a number of clinical studies [3, 4]. However, till now, clinical recommendations for raised Lp(a) reduction are absent. Of currently available lipid-lowering drugs, only proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors mildly decrease Lp(a) level with modest additional effect on relative risk of coronary or cardiovascular events development [5, 6]. New developed antisense oligonucleotides affect the synthesis of apo(a) in the liver and consequently reduce plasma Lp(a) levels. A recent multicenter trial phase 2b included 286 patients with pre-existing CVD and baseline Lp(a) > 60 mg/dL (150 mmol/L) and showed that AKCEA-APO(a)-$L_{Rx}$ (IONIS-APO(a)-$L_{Rx}$) resulted in a dose-dependent reduction of Lp(a) with the maximum effect of 80% at 20 mg weekly [7].

Recently, several large Mendelian randomization studies convincingly demonstrated that to obtain the significant

This article is part of the Topical Collection on *Nonstatin Drugs*

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reduction of MACE in a secondary prevention setting, we have to decrease Lp(a) level by 50–100 mg/dL sustainable for several years [8–10].

Lipoprotein apheresis (LA) is the only available option to gain this aim [11, 12]. LA is usually applied to treat patients at high risk of cardiovascular events when drug therapy is not sufficient or if patients are intolerant to the lipid-lowering drugs.

Lp(a) hyperlipoproteinemia is the indication for therapeutic apheresis in Germany, Austria, the UK, the USA, Canada, and Russia in the treatment of FH patients [13–17•]. However, LA is indicated for the treatment of patients with Lp(a) above 60 mg/dL and ASCVD, despite the control of other risk factors, including LDL cholesterol [18•, 19] only in German National guidelines. More than 2000 patients in Germany received LA using various currently available systems. About 30% of these patients were treated due to the isolated Lp(a)hyperlipoproteinemia [20]. In Italy, Lp(a)hyperlipoproteinemia in combination with the early-onset coronary heart disease has been accepted as the indication for LA since 2009 by the interdisciplinary council of experts, but health authorities have not recognized it [21]. In Russia, LA is recommended for patients with homozygous or heterozygous FH in combination with Lp(a) > 60 mg/dL and early onset of ASCVD [22].

## Non-specific Lp(a) Apheresis

General characteristics of different available systems for LA are presented in Table 1. They can be divided into specific system that remove only Lp(a) and non-specific systems which eliminate all apoB-100 containing lipoprotein particles (Fig. 1.)

Due to the presence of the apoB-100 molecule in the Lp(a) particle, the majority of the all LA systems originally designed for LDL removal can reduce the Lp(a) level by combined removal of both LDL and Lp(a) particles, based on their high structural similarity.

Currently, seven systems are available and used for plasma or whole blood perfusion and able to remove Lp(a) from the human blood (Table 1). Some of them are actively applied in clinical practice, while the others are not yet broadly used.

According to the principle of removal of apoB100-containing lipoproteins, all these systems can be divided into three groups:

Group 1 - based on the separation of the components depending on their physical properties such as size and molecular weight. These systems include membrane cascade plasma filtration, thermofiltration, or lipid filtration—Evaflux® (Kawasumi, Japan), Cascadeflo EC® (Asahi Kasei Medical Co, Japan), and membrane filtration optimized novel extracorporeal treatment (MONET) (Fresenius Medical Care, Germany).

Group 2 - based on the ion exchange interactions (heparin-induced extracorporeal LDL precipitation—HELP® (Plasmat Futura, B. Braun, Germany); adsorption on sorbents with polyanions, for instance, dextran sulfate—Liposorber LA® and Liposorber D® (Kaneka Corporation, Japan); or polyacrylate—DALI® (Fresenius Medical Care) and Lipocollect 200® (Medicollect, Germany)).

Group 3 - immunosorbents with the specific sheep polyclonal antibodies against human LDL—LDL TheraSorb® (Miltenyi Biotec, Germany) and LDL Lipopak® (POCARD, Russia).

Among all of these systems for lipoprotein apheresis, only DALI® and Liposorber D® were designed for the whole blood perfusion (hemoperfusion). The other systems are suitable for removal of lipoproteins only from human plasma, i.e., obligatory require an additional stage of separation of blood cells and plasma.

The method of cascade plasma filtration or double filtration plasmapheresis (DFPP) has been proposed in 1980 to remove LDL [28] and is now also widely used for treatment of patients with FH in Europe, the UK, Australia, Malaysia, New Zealand, and Russia [23, 29] and can be used for semi-selective removal of Lp(a). The system contains two hollow filters differing in pore size. Currently, the widely used Lipid Filter EC-50 (Asahi Medical, Japan) and Octo Nova (Diamed, Germany) plasma separators allow the thermostating of plasma before the cascade plasma filtration, resulting in significant reduction of non-specific losses of plasma proteins and HDL, and also increase the number of removed LDLs [30].

A relatively new system for lipoprotein filtration MONET® also provides an effective removal of apoB100-containing lipoproteins [26, 31]. Prospective observation of 44 patients from 11 centers treated by apheresis using the MONET system (1297 sessions) showed that the relative decrease in LDL-C level was 64.1% (60.8; 67.5), while the Lp(a) concentration reduced by 65.0% (63.7; 70.3). The decrease in the HDL-C level for MONET system exceeded the same for DALI (22.6%, [19.3; 25.8] vs 15.0% [13.2; 16.8], respectively) [26].

Heparin-induced extracorporeal LDL precipitation (HELP) method was proposed in 1983 by Wieland [32]. The method is based on the ability of apoB100-containing lipoproteins to interact with polyanions, such as heparin, forming the complexes that are insoluble at approximate pH of 5.2 and can be separated [33]. Usually, 2.5–3 L of plasma are processed during one procedure, resulting in the lowering of LDL-C and Lp(a) levels by an average of 60% [34, 35] and fibrinogen by 50% [33]. This method is used in Europe, the UK, and rarely

**Table 1** General characteristics of different available systems for lipoprotein apheresis

| Composition/principle of interaction | Procedure abbreviation | Device or procedure commercial name | Manufacturer | Applying* | Removal (%)** | | Suitable for perfusion of | Usage |
|---|---|---|---|---|---|---|---|---|
| | | | | | LDL | Lp(a) | | |
| Anti-apo(a)-agarose/antigen-antibody | Lp(a) IA | Lp(a) Lipopak® | POCARD Ltd., Russia | Russia, EC[#], UK[#] | 7 | 59–88 | Plasma | Multiple |
| Anti-apoB-agarose/antigen-antibody | LDL IA | LDL Lipopak® | POCARD Ltd., Russia | Russia, EC[#], UK[#] | 62–69 | 25–71 | | |
| | | LDL TheraSorb® | Miltenyi Biotec, Germany | EC, Turkey | | | | |
| Polyacrylate-coated polyacrylamide/ ion exchange | DALI | DALI® | Fresenius Medical Care, Germany | EC, UK | 52–76 | 28–74 | Whole blood | Single |
| Polyanion silica/ ion exchange | - | Lipocollect® | Medicollect, Germany | EC[#] | 61 | 61 | Plasma | Multiple |
| Dextran sulfate cellulose/ ion exchange | DSA | Liposorber LA® | Kaneka, Japan | EC, UK, USA, Japan | 49–75 | 19–72 | Plasma | Multiple during one procedure |
| | | Liposorber DL® | | EC, UK, Japan | | | Whole blood | Single |
| Heparin/ ion exchange and precipitation | HELP | HELP® | B Braun, Germany | EC, UK, Russia | 55–69 | 45–61 | Plasma | |
| Hollow fiber/ size base filtration | DFPP | Evaflux® | Kawasumi Laboratories Inc., Japan | EC, UK, Australia, Japan, China, Malaysia, New Zealand, Russia | 56–62 | 53–59 | Plasma | |
| | | Cascadeflo EC | Asahi Kasei Medical Co., Japan | | | | | |
| | | MONET® | Fresenius Medical Care, Germany | EC | 64 | 65 | | |

It is difficult to compare efficacy of different apheresis system in clinical conditions due to the following: variability of plasma treated volume, plasma flow rate, procedure durations, sampling and measurements, etc.

*Abbreviations*: *Lp(a) IA* lipoprotein(a) immunoadsorption, *LDL IA* low-density lipoprotein immunoadsorption, *DSA* dextran sulfate adsorption, *HELP* heparin-induced extracorporeal LDL precipitation, *DFPP* double filtration plasmapheresis, *DALI* direct adsorption of lipoproteins, *MONET* membrane filtration optimized novel extracorporeal treatment

*The data are presented according to the analysis of publications [23–25]

**Data are present as minimal and maximal percent of Lp(a) and LDL removal, which were published in different clinical studies (adapted from [26, 27])

[#] There are currently no data on registration and applying in designated countries

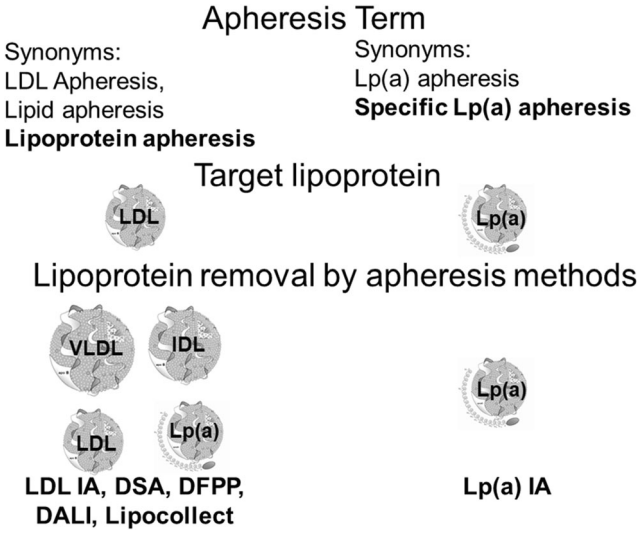


**Fig. 1** Terminology used for the methods to treat patients with drug resistant dyslipidemia. Abbreviations: Lp(a) lipoprotein(a), LDL low density lipoprotein, IDL intermediate density lipoprotein, VLDL very low density lipoprotein, IA immunoadsorption, LDL IA low density lipoprotein immunoadsorption, DSA dextran sulfate adsorption, HELP heparin-induced extracorporeal LDL precipitation, DFPP double filtration plasmapheresis

in Russia; in the USA, the application of this method was discontinued several years ago [24•].

The ability to remove atherogenic lipoproteins using columns with dextran sulfate (DS) cellulose was firstly shown in Watanabe rabbits in 1984 [36]. Currently, during the lipid apheresis with the Liposorber LA15® system, the so-called twin technology with a pair of columns applied to each patient is used: while plasma of patients passes through one column, the other one is regenerating. Thus, the number of removed atherogenic lipoproteins is limited only by the duration of the procedure; the average volume of treated plasma during a single procedure ranges from 4 to 12 L. Such procedure in patients with FH resulted in the decrease of LDL-C by 75–80% and Lp(a) by 40–72% [37].

The first results on the application of columns called Lipocollect 200® (Medicollect, Rimbach, Germany) in the clinical practice have appeared about 10 years ago [38]. The columns contain sterilizable silica gel without any biological components as active ingredients. The columns can be reused and regenerated with the ADAsorb regeneration system (Medicap Ulrichstein, Germany). A study published by Stefanutti et al. presented the data on 50 apheresis procedures for two patients with CHD with a hyperLp(a) and LDL-C > 100 mg/dL. About 3 to 4 L of patients' plasma were treated with an average of 6 cycles per procedure. The relative removal of Lp(a) and LDL-C was about 62% [38]. However, now those columns are not commonly used in clinical practice.

Direct adsorption of lipoproteins consisting of a system designed to perfuse whole blood without a plasma separation stage to remove atherogenic lipoproteins was firstly described in 1993 [39]. The system was called DALI® and manufactured by Fresenius Medical Care (Germany). The patient's blood passed through a column containing polyacrylamide macrobeads with immobilized polyacrylate. Adsorption of LDL-C and Lp(a) is carried out through the interaction of negatively charged functional groups on the sorbent with cations of the apoB100 molecule, similarly to the HELP® systems and Liposorber®. Using the DALI® system, LA reduces the level of Lp(a) by up to 60% when treating the maximum of 1.5 volumes of circulating blood or 5–10 L [40, 41]. Such type of system is used in Europe and the UK.

The earliest reports on the development of another hemosorbent appeared in Japan in 2002. Column was based on DS linked to the cellulose beads enhanced to 240 μm that was suitable for the whole blood perfusion [42]. The data on the treatment of over 20 patients by hemoperfusion with LiposorberD® columns demonstrated the decrease of LDL-C level to 51–75% and Lp(a) level up to 73% without any severe side effects at about 8 L of treated blood [43]. A direct comparison of the two Liposorber systems based on DS for plasma (LA 15) and hemosorption (DL100) in similar conditions and in the same patients demonstrated a decrease in TC, LDL-C, and Lp(a) levels by 59%, 79%, and 87% for hemosorbent and 51%, 65%, and 73% for plasmosorbent [44], which corresponded with and even exceeded the previous data [39, 45]. Liposorber D® is used in Japan and the UK, especially for treatment of patients with hyperLp(a) [29].

The use of macrobeads sorbent for perfusion of the whole blood (DALI® and Liposorber D®) can substantially simplify the lipid apheresis procedures by excluding the fractionation stage. Nevertheless, the single usage of such systems necessitates the design of columns of significantly larger volume; thus, an almost equally effective decrease in LDL-C level for the Liposorber D® and Liposorber L® columns is achieved by using of columns with the volumes of 1100 mL and 150 mL [46].

Therefore, despite the simplified usability, such systems for hemoperfusion as DALI are not the best recommendation for the treatment of patients with severe Lp(a) hyperlipoproteinemia [47].

The administration of angiotensin-converting enzyme (ACE) inhibitors is a direct contraindication to the LA with DALI, Liposorber (both for plasma and hemoperfusion), and DFPP due to the development of hypotensive reactions during activation of the kinin–kallikrein system [18, 48].

Immunosorption provides the most specific systems for removal of LDL and Lp(a) from human plasma with columns containing agarose beads with sheep polyclonal antibodies against apolipoprotein B100 as a ligand used in LDL TheraSorb® (Miltenyi Biotec, Germany) and LDL Lipopak® (POCARD, Russia). The volume of plasma treated by one column varies from 600 to 800 mL. The application of two columns and twin technology together with the multiple

use of column capable of regenerating for up to 100 cycles [49] make it possible to achieve practically unlimited binding capacity and effectivities with high specificity to apoB100-containing lipoproteins. However, the data on the degree of decrease in Lp(a) level during LA with immunosorption columns are quite contradictory and vary from 26 [50] to 74% [51], with an average of 50–60% [52]. It is obvious that the efficiency of Lp(a) removal by columns with an apoB100-specific immunosorbent depends on the ratio of the Lp(a) and LDL concentrations and the volume of the treated plasma. The decrease in Lp(a) concentration as a rule reached 50–60% during the immunosorption [53].

The main disadvantage of the immunosorption columns is the presence of animal origin component. According to modern concepts, this creates additional risks for the patient. However, there have not been reported any specific side effects during the procedures associated with the antibodies-containing carrier in any of the studies conducted over the last 30 years [52, 54].

The data accumulated during the previous decades of using LA for the correction of elevated levels of Lp(a) demonstrate that all described systems for apheresis do not significantly differ in safety and efficiency [54–58].

The first prospective multicenter study that involved 120 patients with elevated Lp(a) who received LA on the top of maximal lipid-lowering therapy showed the 86% reduction of cardiovascular events [59]. Over the past decade, several more single- and multicenter studies have been conducted and published. These studies have demonstrated the significant reduction of major adverse cardiovascular events (MACE) by 74–97% with LA in the treatment of patients with elevated Lp(a) and ASCVD [27, 60]. Two German studies, which showed 78% MACE reduction, included patients with isolated Lp(a) hyperlipoproteinemia [61, 62] and achieved target LDL cholesterol level with lipid-lowering drugs. The results of the multicenter prospective Pro(a)LiFe study [63, 64] and the analysis of the German Lipoprotein Apheresis Registry (GLAR) [65] with the 5-year follow-up period proved the association between decreasing Lp(a) concentration and reduction of MACE owing to regular LA.

Data from 79 German apheresis centers, based on more than 27,000 LA sessions with 1632 patients, allowed to retrieve the group of 303 patients with Lp(a) > 60 mg/dL and LDL-cholesterol < 100 mg/dL. Regular LA led to the 83% reduction in MACE and the 63% reduction in major adverse non-cardiovascular events (MANCE) in the first 2 years of treatment followed by persistence of this effect for the next 5 years [66, 67••].

A recently published KUMC study from the University of Kansas Medical Center (USA), aimed to assess the clinical significance of regular lipoprotein apheresis from 8 to 105 months (mean 48 months) in 14 patients with mean Lp(a) level of 138 mg/dL and mean LDL-C level of 80 mg/dL, showed a 94% decrease in MACE (from 36 to 2) [24•]. The atherosclerotic lesions of peripheral arteries are found in almost half of the patients with Lp(a) hyperlipoproteinemia and indications for LA [68]. According to the Pro(a)LiFe, data for major adverse limb events (MALE) such as angioplasty, stenting, or shunting bypass surgery of arteries of lower extremities reduced from 30 during for 2 years before the initiation of LA to 11 events during 2 years of LA treatment [61]. A similar decrease of MALE was described in a retrospective single-center study of 35 patients with Lp(a) hyperlipoproteinemia [20].

The ankle-brachial index increased from 0.5 ± 0.2 to 0.9 ± 0.1 ($p < 0.001$) after 1 year of regular LA, and the walking distance increased from 87 ± 60 m to 313 ± 145 m over the first year and up to 402 ± 119 m after 2 years ($p < 0.001$). Pain also alleviated significantly from 7.0 ± 1.5 points initially to 1.6 ± 0.7 after 1 year and 1.1 ± 0.4 points after 2 years of LA [69•]. Thus, LA was an effective method for treating patients with Lp(a) hyperlipoproteinemia and severe peripheral arteries atherosclerosis [70••].

Due to the influence of LA on the entire spectrum of atherogenic lipoproteins (Lp(a), LDL, and VLDL), as well as on a wide range of inflammatory, thrombotic, and other biologically active molecules [71, 72], prominent clinical effect of therapeutic apheresis effect in patients with Lp(a) hyperlipoproteinemia could be explained by pleiotropic features. Nevertheless, the analysis of a number of studies of LA in patients with different levels of Lp(a) and LDL-C suggests greater apheresis effectiveness in subjects with isolated elevated Lp(a) concentration [59, 73–75].

The positive clinical effects of apheresis on the state of ASCVD may also be associated with a change in thrombotic status. A recent small randomized controlled cross-over study ($n = 20$) of the effect of LA with Liposorber DL-75 columns in patients with Lp(a) above 50 mg/dL and refractory angina showed the significant decrease in platelet activation and an improvement in endothelial fibrinolysis accompanied by a decrease of von Willebrand factor and fibrinogen [76••]. The primary publication of this study described positive clinical effects of 3-month LA: improving myocardial perfusion, atheroma burden, exercise capacity, and angina symptoms [77]. In a recent kinetics study of 13 patients with Lp(a) concentration > 50 mg/dL and coronary artery disease, it was shown that on regular LA, the fractional catabolic rate of Lp(a) was significantly lower than that of LDL-apoB, whereas production rate did not differ [78].

A common opinion that effective lowering of LDL-C levels by PCSK9 inhibitors may terminate necessity of LA procedures for 60% of patients [79] must be proved in the nearest future. However, the results of the German study [80••] did not confirm this. An open cross-sectional multicenter study included 110 very high-risk patients with established ASCVD and hypercholesterolemia and partially concomitant

Lp(a) hyperlipoproteinemia. Lipid-lowering therapy was revised to achieve the target level of LDL-C by the administration of PCSK9 inhibitors, LA, or their combination. PCSK9 inhibitors reduced Lp(a) levels by 5.6% ± 14.8% [80••], confirming the results of ODYSSEY ESCAPE with the decrease in Lp(a) by 5.0% ± 5.9% on alirocumab [81]. Unfortunately, 32 patients (29.1% of the group size) stopped PCSK9 inhibitor using: 7 patients turned out to be non-responders and 25 stopped taking the drug due to side effects [80••]. These results demonstrate that it is early to talk about the termination of apheresis in very high-risk patients whose clinical condition is stabilized by regular LA. Unlike PCSK9 inhibitors [82], there is a positive effect of LA on vascular inflammation assessed by positron emission tomography [83].

It is suggested that for patients with isolated marked Lp(a) elevation and progressive ASCVD, LA would be a more appropriate therapy than the use of therapeutic monoclonal antibodies against PCSK9 [84]. In a small study of 9 patients with ASCVD, it was shown that in patients with Lp(a)hyperlipoproteinemia, LA was more effective than PCSK9 inhibitors in reducing Lp(a), i.e., 69% versus 12% [85, 86••]. A retrospective cohort study at one LA site in the USA revealed 14 ASCVD patients with isolated elevated Lp(a). LA therapy allowed to reduce MACE by 94% over a mean period of 4 years [24•].

## Specific Lp(a) Apheresis

More than 30 years ago, it has been suggested by our group that specific elimination of Lp(a) alone could lead to regression of atherosclerosis in case if Lp(a) involved in the atherosclerotic plaque's formation. To prove Lp(a) atherogenicity, we have designed immunosorbent with monospecific polyclonal antibodies against human Lp(a) according to the method earlier developed for preparation of specific immunosorbent for extracorporeal LDL elimination [87, 88]. Anti-Lp(a) immunosorbent was highly specific to Lp(a) and almost did not affect LDL and other components of plasma. LDL is practically not removed by the immunosorbent with immobilized anti-Lp(a) antibodies, which has been shown both in vitro experiments and during the Lp(a) apheresis procedures [87, 89, 90]. The decrease in LDL-C does not represent the removal of LDL, but only the removal of cholesterol in Lp(a) particle. For patients with a normal or low level of LDL, this proportion can be significant as it can be seen in patients treated with modern hyperlipidemic medication [12, 91, 92] or lipoprotein apheresis with non-specific Lp(a) systems [24]. Columns with this immunosorbent—"Lp(a) Lipopak®" (POCARD, Russia)—were approved for clinical use, and the therapeutic procedure was called "Lp(a) apheresis" [55]. The first procedures of specific Lp(a) apheresis with "Lp(a) Lipopak" columns were conducted in Moscow [89•] and later in Germany [93–96] and the UK [97]. The single procedure of specific Lp(a) apheresis resulted in the decrease of Lp(a) level by 70–80% [89•, 98]. Regular procedures of Lp(a) apheresis for three patients with history of myocardial infarction resulted in the significant increase in exercise tolerance, decrease in angina symptoms, and regression of coronary atherosclerosis according to angiography analysis [89•].

Lp(a) apheresis was then performed during 18-month, prospective open-controlled clinical study that included patients with stable ischemic heart disease [99••]and an elevated Lp(a) level. All subjects should have the following: (a) clinical indications for coronary angiography, (b) Lp(a) level above 50 mg/dL, (c) LDL cholesterol below 2.5 mmol/L, (d) stable atorvastatin dose 20 to 80 mg per day before apheresis initiation. Patients were allocated in a 1:1 ratio to Lp(a) apheresis or non-apheresis groups. Procedures were conducted weekly using Lp(a) Lipopak® columns.

The atorvastatin dose in Lp(a) apheresis and comparison group was 34 ± 13 and 32 ± 10 mg respectively. During the study, all modifiable atherosclerosis risk factors in the whole cohort were under control; LDL-cholesterol adjusted for the Lp(a)-cholesterol was less than 2.0 mmol/L (77 mg/dL). The effect of Lp(a) apheresis resulted in a 73 ± 12% reduction in Lp(a) concentration. The mean value of the Lp(a) after apheresis sessions was 29 ± 16 mg/dL, whereas the mean interval value was 73 mg/dL. The LDL-cholesterol level corrected for Lp(a)-cholesterol did not differ between the groups. The mean coronary artery diameter stenosis decreased after 18 months by 5.05 ± 12.38% in the Lp(a) apheresis group and increased by 5.04 ± 11.43% in the control group ($p < 0.01$ for the change from baseline in each group; $p < 0.001$ for the between-group comparison) [99••]. Median total atheroma volume assessed by intravascular ultrasound, reduced by − 4.60 $mm^3$ (95% confidence interval, − 13.19 to − 1.81, $p = 0.001$) with apheresis and was unchanged in controls. According to the of virtual histology, the significant decrease in fibrous and fibro-lipid plaque components was found in the apheresis group, but not in the control group. Calcified areas in the apheresis group increased by 2.2 ± 3.1% from baseline and remained unchanged − 0.8 ± 4.9% in the control group ($p <$ 0.03 between the groups) [100••].

Hence, for the first time in a controlled trial, it was shown that sustained and prolonged Lp(a) lowering by specific Lp(a) apheresis, without affecting other plasma components and LDL, led to stabilization and even regression of coronary atherosclerosis with decreases in fibro-lipid and fibrous plaque components. Thus, specific Lp(a) apheresis can be used for the patients with target LDL-cholesterol level, without or with lipid lowering drug therapy, and solo elevated Lp(a) level. Totally, 56 patients with solo elevated Lp(a) have received specific Lp(a) apheresis procedure without any serious complications.

## Conclusion

At present, specific Lp(a) apheresis is the only possible method that solely targets Lp(a) and reduced elevated Lp(a) level with high efficiency. In most countries, non-specific lipoprotein apheresis is used for Lp(a)hyperlipoproteinemia in very high-risk subjects with progressive ASCVD. PCSK9 inhibitors have only modest effect on significantly elevated Lp(a), whereas large population-based studies warranted profound reduction Lp(a) levels to obtain long-term improving the atherosclerosis course. New generation of Lp(a) lowering drugs could arrive in a few years.

## Compliance with Ethical Standards

**Conflict of Interest** Dr. Pokrovsky has nothing to disclose.
Dr. Afanasieva has nothing to disclose.
Dr. Ezhov has nothing to disclose.

**Human and Animal Rights and Informed Consent** This article does not contain any studies with animals. In our own human studies, all subjects provided written informed consent.

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- • Of importance
- •• Of major importance


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Suppl. 2013;14(1):93–9. https://doi.org/10.1016/j.atherosclerosissup.2012.10.015 **The first controlled clinical trial showed that the specific and sustained removal of Lp(a) leads to diminishing signs of coronary atherosclerosis**.

100.•• Pokrovsky SN, Afanasieva OI, Safarova MS, Balakhonova TV, Matchin YG, Adamova IY, et al. Specific Lp(a) apheresis: a tool to prove lipoprotein(a) atherogenicity. Atheroscler Suppl. 2017;30:166–73. https://doi.org/10.1016/j.atherosclerosissup.2017.05.004 **The results of a study of the effect of specific Lp(a) apheresis on the dynamics of clinical and instrumental indicators of atherosclerotic lesions in the coronary and carotid arteries, as well as the dynamics of biochemical parameters of inflammation over 18 months of apheresis, are summarized**.