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Background—Lipoprotein(a) (Lp(a)) hyperlipoproteinemia is a major risk factor for cardiovascular disease, which is not affected by treatment of other cardiovascular risk factors. This study sought to assess the effect of chronic lipoprotein apheresis (LA) on the incidence of cardiovascular events in patients with progressive cardiovascular disease receiving maximally tolerated lipid-lowering treatment.

Methods and Results—In a prospective observational multicenter study, 170 patients were investigated who commenced LA because of Lp(a)-hyperlipoproteinemia and progressive cardiovascular disease. Patients were characterized regarding plasma lipid status, lipid-lowering drug treatment, and variants at the LPA gene locus. The incidence rates of cardiovascular events 2 years before (y-2 and y-1) and prospectively 2 years during LA treatment (y+1, y+2) were compared. The mean age of patients was 51 years at the first cardiovascular event and 57 years at the first LA. Before LA, mean low-density lipoprotein cholesterol and Lp(a) were 2.56 ± 1.04 mmol·L^{-1} (99.0 ± 40.1 mg·dL^{-1}) and Lp(a) 3.74 ± 1.63 µmol·L^{-1} (104.9 ± 45.7 mg·dL^{-1}), respectively. Mean annual rates for major adverse coronary events declined from 0.41 for 2 years before LA to 0.09 for 2 years during LA ($P<0.0001$). Event rates including all vascular beds declined from 0.61 to 0.16 ($P<0.0001$). Analysis of single years revealed increasing major adverse coronary event rates from 0.30 to 0.54 ($P=0.001$) for y-2 to y-1 before LA, decline to 0.14 from y-1 to y+1 ($P<0.0001$) and to 0.05 from y+1 to y+2 ($P=0.014$).

Conclusions—In patients with Lp(a)-hyperlipoproteinemia, progressive cardiovascular disease, and maximally tolerated lipid-lowering medication, LA effectively lowered the incidence rate of cardiovascular events.

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Key Words: blood component removal ■ cardiovascular diseases ■ coronary disease ■ lipoproteins ■ prevention & control

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Concentration of low-density lipoproteins (LDL) is the best established risk factor of coronary artery disease (CAD). Evidence from prospective epidemiological studies has accumulated to firmly document an association of elevated circulating levels of lipoprotein(a) (Lp(a)) with cardiovascular disease (CVD) including CAD, cerebrovascular disease, and

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peripheral artery disease.[1–3] Lp(a) is considered to play an independent active causal role in vascular inflammation and atherothrombosis.[4,5] Therefore, effective and safe Lp(a)-lowering therapies should have the potential to lower cardiovascular risk.[2] Lp(a) levels are highly heritable. Two common variants in LPA, the gene encoding apolipoprotein(a), rs10455872 and rs3798220 have been found to be associated with CAD risk at odds ratios of 1.70 and of 1.92, respectively.[6]

Lipoprotein apheresis (LA) is the final escalating option to lower blood LDL levels in severely hypercholesterolemic patients who have familial hypercholesterolemia or other forms of hypercholesterolemia resistant to or intolerant of lipid-lowering medication.[7] There are several methods of LA using different physicochemical principles, ie, filtration, precipitation, or adsorption, to reduce LDL particles by 60% to 70% from baseline during a single treatment session.[7]

Since 1991 reimbursement of LA has been implemented in guidelines of statutory health insurance funds in Germany. Primary prevention for homozygous familial hypercholesterolemia and secondary prevention for heterozygous familial hypercholesterolemia or severe forms of hypercholesterolemia associated with progressive clinical courses are indications for chronic treatment after approval by committees of regional associations of statutory health insurance physicians.[8] The ability of LA methods to lower Lp(a) as effective as LDL-cholesterol (LDL-C) led to encouraging pilot experiences in a small number of patients with Lp(a)-hyperlipoproteinemia (Lp(a)-HLP) and strikingly progressive CAD. Consequently, in 2008, the German Federal Joint Committee decided to add Lp(a)-HLP as an indication for chronic LA with regular reimbursement.[9] The German Federal Joint Committee stipulated with the new reimbursement guideline that additional prospective data are required to prove efficacy of LA for this indication and to justify maintenance of the decision.

A longitudinal cohort study for the first time characterized this subgroup of CVD patients confined to CAD cases before the current reimbursement guideline was established.[10] A total of 120 patients were included. Mean Lp(a) concentration before commencing LA was 4.21 ± 1.50 µmol·L^{-1} (117.9 ± 42.0 mg·dL^{-1}). The mean annual major adverse coronary events (MACE) rate per patient was 1.06 before versus 0.14 during LA treatment ($P<0.0001$). This difference was impressive, but the study has several weaknesses. Basically, all patients in this study were approved for chronic LA owing to severe hypercholesterolemia only excluding proven familial forms. Concomitant elevation of Lp(a) was not necessarily regarded as the major risk factor in these patients. Further criticisms were selection of patients, lack of prespecified prospective observation, and highly variable individual observation periods before (5.5 ± 5.8 years) as well as during (5.0 ± 3.6 years) chronic LA. The results, however, were sufficient to raise ethical concerns about withholding LA in such particularly high-risk patients if assigned to the control group of a randomized trial. The protocol of a randomized, controlled trial had been suggested, but it failed to achieve ethical approval in Germany. Investigating a concurrent control group of the same patients not treated by LA was regarded not feasible. A candidate patient would unlikely agree to be assigned to an observation group facing his potential risk and knowing about the possibility of LA reimbursement.

Therefore, the best way to generate new prospective data in the field was a prospective observational study comparing the incidence rates of cardiovascular events in patients with Lp(a)-HLP and progressive CVD retrospectively before and prospectively after commencing chronic LA with a prespecified uniform observation period. The aim was to fulfill demands of the German Federal Joint Committee and further investigate the putative causal role of Lp(a) for CVD.

Methods

Study Design

A prospective observational multicenter study was conducted including 28 treatment sites throughout Germany. The underlying hypothesis for the before and after design was that the incidence rate of cardiovascular events in a prespecified observation period is the net effect of progression of CVD and efficacy of concurrent treatment. Timelines included a 2-year retrospective (y-2, y-1) and 2-year prospective (y+1, y+2) period and an additional follow-up period of 2 further years (y+3, y+4) (Figure 1). Observation periods were determined by the day of the first LA as day zero. Inclusion in the study had no impact on individual treatment regimens. Descriptive analysis included baseline characteristics and 6-month or annual status records for the retrospective and prospective parts. The study was approved by an ethical committee (No. 011/1504, International Ethics Committee, Freiburg, Germany) and reported to an open-source online registry (No. DRKS00003119, German Clinical Trials Register, Freiburg, Germany). All participants gave written informed consent.

Patient Recruitment and Eligibility Criteria

The sole criterion for patient enrollment was approval and subsequent commencement of chronic LA owing to isolated Lp(a)-HLP and progressive CVD by the apheresis committee of the regional association of statutory health insurance physicians, or directly by the individual statutory or private health insurance fund according to German reimbursement guidelines. The following parts of this guideline are essential for baseline characteristics of patients enrolled in this prospective study[8,9]:

> *§1 Aim and Contents: (1) This guideline governs the requirements for performance and reimbursement of apheresis as part of statutory health care as well as assessment and approval of indications for apheresis based on a case by case review. (2) For the diseases listed in §3 statutory health care provides in the majority of cases highly effective drug treatment as standard of care. Apheresis shall be considered as last resort in exceptional cases exhibiting refractory clinical courses. §3 Indication: (2) LDL-apheresis for isolated Lp(a)-elevation may be only performed for patients with isolated Lp(a)-elevation above >2.14 µmol·L⁻¹ (60 mg·dL⁻¹) and LDL-cholesterol in normal range and progressive cardiovascular disease (coronary artery disease, peripheral arterial occlusive disease or cerebrovascular disease) as documented clinically and by imaging techniques. Careful consideration of the entire risk profile of the patient shall have superior priority for approval of the indication. [Translated from German]*

Lp(a)-HLP should be isolated in the sense that all other cardiovascular risk factors have to be under individually optimized treatment.[8,9] The threshold of 2.14 µmol·L^{-1} (60 mg·dL^{-1}) for Lp(a) was supported by the European Consensus Panel recommending a desirable level below the 80th percentile, ie, <1.79 µmol·L^{-1} (50 mg·dL^{-1}).[4] The reimbursement guideline has no exclusion criteria regarding comorbid conditions and no criterion of an explicit number or frequency of events. However, all aspects are considered during the case by case review. No reassessment of patients' approval was performed before enrollment by the study group. The approval must be extended on an annual basis by applications for renewal. All enrolled patients were reevaluated at least once during the study period. The date of actual start of chronic LA in a single patient was determined by the clinical course including previous diagnostic examinations and treatment and the time of the approval process, which could vary between weeks and months. The actual date of the first LA was not influenced by enrollment in the observational study. All participating centers confirmed that all consecutive patients commencing chronic LA because of Lp(a)-HLP were enrolled during the study period. The start of the enrollment period for Pro(a)LiFe was set at January 2008. Based on the sample size calculation, patient enrollment was completed on August 2010 with 171 enrolled patients (Figure 1).
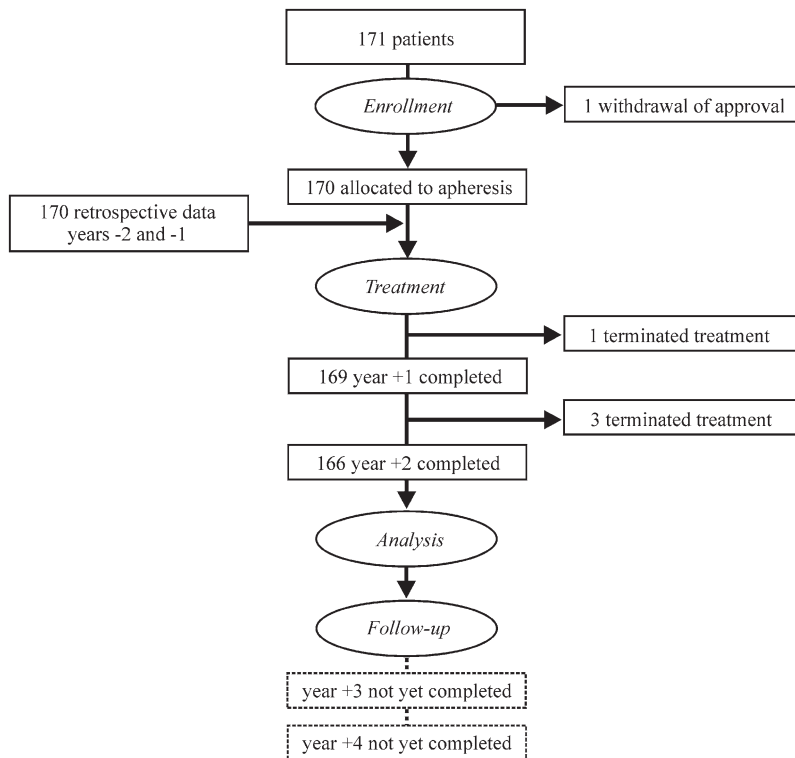
Figure 1. Trial flow diagram with numbers of patients.

Data Management

Study sites received standardized case report forms for data collection based on original patient records. At the time of enrollment, patients' baseline characteristics were recorded including demographic data, medical history, first diagnosis and status of CVD, family history of CVD, medication, and concomitant diseases. Filed applications for reimbursement of chronic LA summarizing complete clinical courses of CVD in every individual patient, including all primary reports on hospitalization for cardiovascular events, diagnostic imaging, or therapeutic interventions, were used for retrospective analysis. Applications had been reviewed by committees of regional associations of statutory health insurance physicians or, in some cases, directly by the individual health insurance fund. Data were documented annually for outcome parameters, medication, status of CVD, and concomitant diseases in both the retrospective and prospective parts of the study. Laboratory data were documented annually in the retrospective part and every 6 months in the prospective part, starting with first LA treatment (see Table 1 and Table 2). Treatment modality, vascular access, treated plasma or blood volume, frequency of treatment, and anticoagulation were also assessed every 6 months. Occurrence of serious adverse events was collected every 6 months in the prospective part. An independent data and safety-monitoring board was established for scientific supervision of data assessment and data validation (see list of study group members in the Appendix).

Lipoprotein Apheresis

Standard selective LA procedures used during this study have been described in the literature,[7] and were performed according to manufacturers' instructions: temperature-optimized double-filtration plasmapheresis (Lipidfiltration, Asahi Kasei Medical, Japan and Octo Nova, Diamed Medizintechnik, Cologne, Germany), heparin-induced LDL precipitation apheresis (HELP, Plasmat Futura; B.Braun, Melsungen, Germany), polyacrylate adsorption from whole blood and simple double-filtration plasmapheresis (DALI and Monet, Fresenius Medical Care, Bad Homburg, Germany), dextran-sulfate adsorption from plasma and whole blood (Liposorber LA and DL systems; Kaneka, Osaka, Japan), and ApoB100 immunoadsorption (TheraSorbLDL, Miltenyi Biotec, Bergisch Gladbach, Germany). The choice of the method was at the discretion of treatment sites.

Laboratory Measurements

LDL-C, Lp(a), total cholesterol, high-density lipoprotein cholesterol, triglycerides, fibrinogen, hemoglobin, creatinine, and hemoglobin A1c in patients with diabetes mellitus were measured in laboratories with long-standing relationships to study sites with no change during the study. All laboratories were certified according to ISO 15189 or ISO/IEC 17025. LDL-C was measured by using direct assay methods throughout. Lp(a) was measured by rate nephelometry assays or specific sensitive immunoassay kits. Lp(a) and LDL-C measurements were additionally supervised by apheresis committees of the regional associations of statutory health insurance physicians as part of the initial and annual renewal application process for LA. Results are expressed as means and standard deviations. Conversion to SI units followed recommendations of the *American Medical Association Manual of Style, 10th ed.*, eg, for Lp(a) mg·dL^{-1} was converted to µmol·L^{-1} by factor 0.0357, and for LDL-C mg·dL^{-1} was converted to mmol·L^{-1} by factor 0.0259.

Reduction rates of LDL-C and Lp(a) were measured before and immediately after LA every 6 months starting with the first LA. Kinetics of the rebound of LDL-C and Lp(a) between 2 consecutive LA sessions follows a sawtooth curve. Time-averaged concentrations (C) for this interval can be estimated by using the empirical equation $C_{\text{interval mean}} = C_{\text{min}} + K(C_{\text{max}} - C_{\text{min}})$, with C_{min} for the concentration immediately after LA, C_{max} for the concentration immediately before the next LA and K set as 0.73.[11,12] Time-averaged concentrations have been suggested as surrogate parameters for mean levels of LDL-C or Lp(a) during chronic LA.[11,12]

Additional informed consent was obtained from patients to perform genetic analysis of the variants rs10455872 and rs3798220 of the LPA locus.[6,13] Genomic DNA was isolated from EDTA whole blood samples from patients with the QIAamp DNA Blood Mini Kit spin procedure (Qiagen, Germany). The isolated DNA was analyzed on an agarose gel and was measured by ultraviolet spectrophotometry at 260 nm. Amplicons spanning the rs10455872 and rs3798220 polymorphic variants were amplified by using forward primers rs104f and rs379f, respectively, and appropriate reverse primers (Perkin-Elmer/Cetus DNA thermocycler 9700). After ExoSap PCR-Clean-up (Affymetrix, Santa Clara, CA) sequencing was performed by using direct terminator sequencing technology (ABI BigDye Terminator_v1; 3130Xl). DNA was analyzed with the SeqPilot software version 3.1 and compared

Table 1. Baseline Characteristics at Time of First LA Treatment

	All Patients (n=170)
Male/female	123 (72.3)/47 (27.7)
Age, y	56.5±10.8
Male, y	56.3±10.5
Female, y	56.9±11.5
Weight, kg	81.2±13.6
Body mass index, kg·m^{-2}	27.3±3.9
Smoking habits	
Never	91 (53.5)
Former	71 (41.8)
Current	8 (4.7)
Coronary artery disease	156 (91.8)
1-/2-/3-vessel coronary disease	27 (15.9)/33 (19.4)/96 (56.5)
Cerebral atherosclerosis	77 (45.3)
Peripheral atherosclerosis	65 (38.2)
Renal artery stenosis	26 (15.3)
Time between first LA and	
First diagnosis of vascular disease, y	6.7±5.2
First vascular event or intervention, y	6.1±6.0
Positive family history	
For CVD in first-degree male/female relatives before age of 55/65 y	87 (51.2)
For cardiovascular, cerebrovascular, or peripheral vascular disease in first-degree male/female relatives before age of 55/65 y	101 (59.4)
Diagnosis of diabetes mellitus, yes/no	37 (21.8)/133 (78.2)
HbA1c of patients with diabetes mellitus, %	6.5±0.6
Treated arterial hypertension, yes/no	125 (73.5)/45 (26.5)
Creatinine, µmol·L^{-1} [mg·dL^{-1}]	106.1±88.4 [1.2±1.0]
Chronic renal failure as assessed by Cockcroft-Gault equation: eGFR, mL·min^{-1}	
≥90	103 (60.6)
60–89	44 (25.9)
30–59	19 (11.1)
15–29	1 (0.6)
<15 or dialysis	3 (1.8)
Hemoglobin, mmol·L^{-1} [g·dL^{-1}]	8.5±1.9 [13.7±3.0]

Values indicate numbers (percentages) or mean ± SD with conventional units in squared brackets. CVD indicates cardiovascular disease; eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; and LA, lipoprotein apheresis.

with reference NG_016147.1. Information from the 2 single-nucleotide polymorphisms was combined into a single LPA genotype.[6,14]

Outcome Parameter

The primary outcome parameter was the mean annual incidence rate of cardiovascular events per patient during the 2 years before commencing chronic LA versus the 2 first years during chronic LA. Because of the exactly prespecified identical time intervals before and after LA for all patients, the rate and documented absolute number of events have an identical meaning. In addition, rates were analyzed for single years. Event rates were calculated for each patient including any event in y-2 and y-1 versus any event in y+1 and y+2.

All cardiovascular events in the year of death including the fatal event were counted in the year of death. Cardiovascular death was not handled with a weight >1 event for calculations. Events or interventions at a specified vascular locus within 28 days were considered as a single event. Events occurring at 2 different vascular loci were counted as 2 events irrespective of the time interval. According to the indication guideline of the German Federal Joint Committee used, cardiovascular events cover coronary, peripheral, and cerebrovascular beds. Because of thrombotic effects exerted by Lp(a), the events of venous thrombosis and pulmonary embolism were also documented. MACE identical to the definition by Jaeger et al[10] was the primary composite outcome parameter, ie, cardiovascular death, nonfatal myocardial infarction, coronary bypass surgery, percutaneous coronary intervention, or stent. Adverse cardiac or vascular events (ACVE) are the secondary composite outcome parameter, defined as the sum of all documented cardiac or vascular events in arterial and venous vascular beds, as well, ie, MACE (see above), or cerebrovascular event (nonhemorrhagic, cerebrovascular event = transient ischemic attack or prolonged reversible ischemic neurologic deficit or ischemic stroke or carotid percutaneous transluminal angioplasty or carotid surgery) or peripheral vascular event (peripheral vascular event of lower extremities or renal arteries = percutaneous transluminal angioplasty, stent, bypass surgery, amputation), or venous thrombotic event = deep venous thrombosis or pulmonary embolism.

Sample Size Calculation and Statistical Analysis

Sample size was calculated to detect a difference in the 2-year incidence rates of MACE. The results of Jaeger et al[10] have been the only available orientation for our sample size calculation with a mean annual rate of MACE of 1.06 before LA and an ≈80% lower rate during LA. Therefore, the mean annual incidence rate of MACE in Pro(a)LiFe was projected to be 1 before LA. A minimum reduction of 30% was regarded as clinically relevant, corresponding to a decline of the rate of 0.3 events per year. A 2-sided level α=0.05 was chosen, with assumption of σ=1 and Δ=−0.3. Aim was to achieve a statistical power of 1−β=0.8, assuming a standardized difference Δ/σ=0.3. With these assumptions, a minimum sample size of 90 patients was calculated to observe a significant difference in MACE between both 2-year periods. Considering that the analysis was nonparametric, and to improve power and precision, the number was increased to 120. The proportion of patients affected by diabetes mellitus or severe renal impairment (estimated glomerular filtration rate <30 mL·min^{-1}) was estimated to be 20% to 25% each. To allow separate analysis of patients with Lp(a)-HLP, excluding both comorbid conditions, the final sample size target was set at 170 patients.

SPSS statistical software package (version 20) was used for analysis. Descriptive analysis of baseline characteristics and 6-month or annual status records was performed by the use of routine methods. Two-sided paired Wilcoxon test was used for MACE and ACVE rates for 2-year and 1-year periods. The incidence rate has the same meaning as absolute total number of events with exactly identical time intervals for all patients. Therefore, for each individual patient, the absolute total number of events was used as a variable for the 2-sided paired Wilcoxon test. Annual rates for components of MACE, ie, myocardial infarction, coronary artery bypass graft, and percutaneous coronary intervention were analogously analyzed. Event rates before and during chronic LA and their differences were used as variables for explorative subgroup analysis. Subgroup analysis of different cutoff levels of Lp(a), LDL-C, comorbid conditions of diabetes mellitus or chronic kidney disease, positive family history, and genetic variants of the LPA gene was performed with the Wilcoxon test or Kruskal-Wallis test. Differences of Lp(a) and LDL-C before and after LA treatments was assessed by the paired Wilcoxon test.

Results

Baseline Characteristics

In total, 171 consecutive patients were enrolled; 170 were studied. One patient was excluded after withdrawal of

Table 2.   Plasma Concentrations of Lipoproteins and Fibrinogen in 2 Years Before and in 2 Years During Steady State of Chronic LA

	y-2	y-1	1st LA	y+1, 6 mo	y+1, 12 mo	y+2, 6 mo	y+2, 12 mo
Lp(a)							
Mean or interval mean level,* µmol·L⁻¹ [mg·dL⁻¹]	3.94±1.77 [110.4±49.6]	3.95±1.61 [110.6±45.1]	3.16±1.35 [88.6±37.8]	2.57±1.05 [72.0±29.4]	2.54±0.99 [71.2±28.1]	2.54±0.99 [71.2±27.6]	2.53±0.96 [70.9±26.8]
C_{max}, before LA,† µmol·L⁻¹ [mg·dL⁻¹]	ND	ND	3.74±1.63 [104.9±45.7]	3.12±1.30 [87.4±36.4]	3.09±1.26 [86.6±35.2]	3.10±1.23 [86.8±34.5]	3.10±1.20 [86.8±33.5]
C_{min}, after LA, †, µmol·L⁻¹ [mg·dL⁻¹]	ND	ND	1.51±0.83 [42.2±23.3]	1.04±0.50 [29.2±14.4]	0.97±0.42 [27.3±11.7]	0.97±0.40 [27.1±11.1]	0.94±0.44 [26.4±12.4]
Reduction, %	ND	ND	59.8±14.1	66.6±11.5	68.5±9.4	68.8±9.5	69.6±9.8
LDL-C							
Mean or interval mean level,* mmol·L⁻¹ [mg·dL⁻¹]	2.56±0.98 [98.7±37.8]	2.57±1.02 [99.2±39.4]	2.17±0.88 [83.7±34.1]	2.13±0.79 [82.3±30.4]	2.09±0.75 [80.6±29.0]	2.15±0.79 [83.0±30.4]	2.10±0.83 [81.1±31.9]
C_{max}, before LA,† mmol·L⁻¹ [mg·dL⁻¹]	ND	ND	2.56±1.04 [99.0±40.1]	2.54±0.92 [98.1±35.5]	2.55±0.93 [98.3±35.9]	2.64±0.96 [101.8±36.9]	2.59±1.05 [100.0±40.6]
C_{min}, after LA,† mmol·L⁻¹ [mg·dL⁻¹]	ND	ND	1.10±0.54 [42.4±20.9]	0.93±0.51 [36.1±19.5]	0.87±0.42 [33.4±16.2]	0.87±0.40 [33.4±15.6]	0.85±0.47 [32.7±18.0]
Reduction, %	ND	ND	57.2±13.2	63.2±12.2	66.0±12.2	67.2±10.2	67.3±9.8
HDL-C,‡ mmol·L⁻¹ [mg·dL⁻¹]	ND	ND	1.35±0.56 [52.3±21.8]	1.33±0.39 [51.4±15.0]	1.30±0.39 [50.0±15.0]	1.31±0.36 [50.6±14.0]	1.28±0.34 [49.5±13.1]
Total cholesterol,‡ mmol·L⁻¹ [mg·dL⁻¹]	ND	ND	4.58±1.30 [176.8±50.2]	4.68±1.28 [176.9±45.2]	4.68±1.28 [180.6±49.3]	4.67±1.15 [180.3±44.3]	4.60±1.18 [177.6±45.4]
Triglycerides,‡ mmol·L⁻¹ [mg·dL⁻¹]	ND	ND	1.92±1.31 [169.8±115.6]	2.09±1.41 [185.2±124.8]	2.24±1.61 [197.8±142.2]	2.11±1.28 [186.3±112.9]	2.12±1.39 [187.5±122.7]
Fibrinogen,‡ µmol·L⁻¹ [mg·dL⁻¹]	ND	ND	10.33±3.99 [351.2±135.6]	9.31±3.18 [316.7±108.1]	9.54±3.34 [324.4±113.7]	9.34±3.12 [317.6±106.1]	9.53±3.30 [324.0±112.3]

Values indicate mean±SD with conventional units in squared brackets. HDL-C indicates high-density lipoprotein cholesterol; LA, lipoprotein apheresis; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein(a); ND, not done; and SD, standard deviation.

*For y-2 and y-1, mean levels represent calculations with the use of retrospective data; for first LA, y+1, and y+2, interval mean levels represent time-averaged concentrations between 2 LA treatments calculated according to Kroon et al.[11]

†Concentrations were measured immediately before or after LA treatments.

‡Concentrations were measured only immediately before LA treatments.

approval for LA by the apheresis committee (Figure 1). At the time of completed enrollment, 170 patients represented ≈60% of all German patients receiving chronic LA owing to elevated Lp(a).[15] Patients' characteristics are summarized in Table 1. Seventy-two percent of 170 patients were male. Mean age at first LA was 56.5±10.8 years. In y+1, 1 patient terminated LA treatment with pelvic fracture and subsequent diagnosis of colon cancer. In y+2, 3 further patients terminated LA treatment: 2, because of a lack of compliance, and 1 after a traffic accident. Therefore, a total of 166 patients could be analyzed prospectively for 2 years during LA (Figure 1).

CVD was first diagnosed at a mean age of 49.8 years and a mean of 6.7±5.2 years before commencing chronic LA. At the time of first LA, 156 (91.8%) patients had CAD, 77 (45.3%) had concomitant or sole cerebrovascular disease, and 65 (38.2%) had concomitant or sole peripheral atherosclerosis. Eighty-seven (51.2%) patients had a positive family history for CVD in first-degree relatives before the age of 55 for men or 65 years for women. In 96 CAD patients (56.5%), 3-vessel disease was present at the time of first LA. Relevant comorbid conditions were diabetes mellitus in 37 (21.8%) and renal failure with an estimated glomerular filtration rate <30 mL·min⁻¹ in 4 (2.4%) patients. At the time of first LA, 73.5% of patients were treated for arterial hypertension.

LA was performed twice per week in 3 (1.8%) patients, weekly in 157 (92.4%) patients, biweekly in 9 (5.3%) patients, and every 3 weeks in 1 (0.6%) patient. For vascular access, peripheral veins were used in 79.9%, arteriovenous fistulas in 20.1%. The distribution of the apheresis methods used and the mean treatment volumes are summarized in Table 3.

Safety of Lipoprotein Apheresis Treatment

Since 1991, LA has had the status of regular reimbursement in Germany. Therefore, safety analysis was not an aim of this study. The entire study period represents a total number of 16 311 treatments, assuming that 5% of scheduled treatment sessions were not performed. No serious adverse events related to LA treatment were observed. Mean plasma concentrations of hemoglobin, creatinine, and fibrinogen stayed within a stable normal range throughout the study. Minor adverse events typically associated with outpatient apheresis treatment, eg, transient hypotension, dizziness, or nausea were not analyzed.

Laboratory Parameters and Medication

Laboratory investigations are summarized in Table 2. Mean Lp(a) concentration before chronic LA was elevated ≈3-fold above the upper limit of normal and was reduced by a single LA treatment by 69.6±9.8% (*P*<0.0001). Mean LDL-C

Table 3.   Distribution of LA Methods and Treated Plasma and Blood Volumes as Assessed in y+2

Treatment Method	Patients	Mean Treated Volume, mL
Methods with plasma separation		Plasma
DFPP, temperature optimized	101 (60.8)	3678±592
Heparin-induced lipoprotein precipitation	16 (9.6)	3306±503
DSA	6 (3.6)	4083±627
DFPP, simple	4 (2.4)	3000±577
ApoB100 immunoadsorption	4 (2.4)	5625±2287
Methods with whole blood treatment		Blood
DSA	24 (14.6)	8713±1230
Polyacrylate adsorption	11 (6.6)	8555±1807

Values indicate absolute numbers (percentages) or mean±SD. DFPP indicates double-filtration plasmapheresis; DSA, dextran-sulfate adsorption; LA, lipoprotein apheresis; and SD, standard deviation.

concentration before LA was ≈2.6 mmol·L^{-1} (100 mg·dL^{-1}). Mean LDL-C reduction was 67.3±10.2% per LA session ($P<0.0001$). Mean reduction rates for both Lp(a) and LDL-C were slightly lower at the first LA treatment because of lower treated plasma or blood volumes.

At first LA, 97% of patients received lipid-lowering medication consisting of statins or a combination of statins with other lipid-lowering drugs (Table 4). Eight patients (4.7%) did not receive any lipid-lowering medication. Their mean LDL-C and Lp(a) before first LA was 3.17±1.06 mmol·L^{-1} (122.4±41.1 mg·dL^{-1}) and 4.21±2.03 µmol·L^{-1} (118.0±56.8 mg·dL^{-1}), respectively. Of these patients 6 were intolerant of statins or ezetimib, 2 patients received statins in y-2 and y-1, but discontinued statins after commencing LA.

Analysis of Events

Comparative analysis of MACE and ACVE rates for 2 years before and first 2 years during chronic LA included 166 patients who completed the 2-year prospective observation period. One cardiovascular death occurred in y+2 in a patient who had critical limb ischemia, end-stage renal disease, and subsequent multiorgan failure. For the analysis, this case was counted as 3 ACVE in y+1 and fatal myocardial infarction in y+2. The mean annual rate of MACE decreased from 0.41 to 0.09 ($P<0.0001$; Table 5) reflecting a 78% proportional reduction of MACE (Figure 2). Analysis of absolute numbers and corresponding rates for single years revealed a significant increase of MACE from y-2 to y-1 ($P=0.001$), followed by a steep decrease from y-1 to y+1 ($P<0.0001$) and further from y+1 to y+2 ($P=0.003$) (Figure 3, Table 6). Follow-up in y+3 and y+4 with continuing LA will be reported separately after completion. The details for MACE components are given in Figure 4.

The mean annual rates and rates in single years of ACVE showed an essentially identical pattern (Figure 3, Tables 5 and 6). Non-MACE type events are reported in Figure 4. Low figures did not allow statistical analysis for events in peripheral and cerebrovascular beds.

Explorative subgroup analysis could not identify any subgroup of patients exhibiting a statistically significant and clinically relevant difference in MACE or ACVE rate patterns before and during chronic LA. Specifically, there were no apparent differences by sex, baseline Lp(a) concentrations broken down by median and quartiles, baseline LDL-C above or below 100 or 70 mg·dL^{-1}. In patients with diabetes mellitus (n=35), event rates also significantly declined after starting chronic LA ($P=0.025$ for MACE, $P=0.001$ for ACVE). The subgroup of 4 patients with CKD stages ≥4, including 3 patients undergoing dialysis, was too small for any separate analysis. Also, no effect of treatment site, history of smoking, positive family history, and body mass index was observed. Most patients were treated with temperature-optimized double-filtration plasmapheresis (n=101; Table 3). In this subgroup, annual rates for MACE (ie, y-2, 0.29; y-1, 0.52; y+1, 0.12; y+2, 0.03) and ACVE (ie, y-2, 0.47; y-1, 0.83; y+1, 0.18; y+2, 0.08) resembled those for the entire cohort. Annual rates for other single methods were almost identical, but patient numbers were too small to perform statistical analysis.

Genetic Analysis of the LPA Locus

Samples from 137 patients were genotyped for the 2 common variants rs10455872 and rs3798220 at the LPA locus on chromosome 6q26-27. There were no statistically significant differences between these 137 patients and the total 170 patients regarding baseline characteristics and event rates before or after commencing LA. Fifty-three patients (38.7%) had neither risk allele; 84 patients (61.3%) had at least 1 or

Table 4.   Changes in Lipid-lowering Medication, Acetylsalicylic Acid, Phenprocoumon, and Antihypertensive Medication

	y-2	y-1	Date of 1st LA	y+1	y+2
Lipid-lowering medication, any	160 (94.1)	165 (97.1)	162 (95.3)	162 (95.3)	154 (92.8)
Statins, alone	68 (40.0)	67 (39.4)	64 (37.6)	61 (35.9)	60 (34.3)
Statins + ezetimib	73 (42.9)	73 (42.9)	74 (43.5)	76 (44.7)	79 (47.9)
Statins + other lipid-lowering medication*	24 (14.1)	27 (15.9)	27 (15.9)	26 (15.3)	27 (16.4)
Nicotinic acid	42 (24.7)	58 (34.1)	47 (27.6)	37 (21.8)	39 (23.5)
Acetylsalicylic acid	157 (92.4)	155 (91.2)	154 (90.6)	153 (90.0)	151 (91.0)
Phenprocoumon	3 (1.8)	5 (2.9)	6 (3.5)	5 (2.9)	6 (3.6)
Antihypertensive medication	123 (72.4)	123 (72.4)	125 (73.5)	128 (75.3)	124 (74.7)

Values indicate numbers (percentages) of patients receiving medication. LA indicates lipoprotein apheresis.
*Fibrates, cholestyramine, or omega-3-acid ethyl esters.

Table 5.   Mean Annual Rates for MACE, ACVE, MI, PCI, and CABG for 2 Years Before (y-2, y-1) and After (y+1, y+2) Commencing Chronic LA and Percentage Changes (Δ) Between Periods Before and During Apheresis

	(y-2 + y-1)	(y+1 + y+2)	Δ, %	P Value
MACE	0.41±0.45	0.09±0.22	−78.0	<0.0001
ACVE	0.58±0.53	0.14±0.31	−75.9	<0.0001
MI	0.14±0.24	0.02±0.10	−85.7	<0.0001
PCI	0.22±0.35	0.07±0.19	−68.2	<0.0001
CABG	0.05±0.15	0.01±0.05	−80.0	0.001

ACVE indicates adverse cardiac or vascular events; CABG, coronary artery bypass graft; LA, lipoprotein apheresis; MACE, major adverse coronary events; MI, myocardial infarction; and PCI, percutaneous coronary intervention.

both risk alleles (Table 7). Three homozygotes were found for rs10455872 (2.2%), no homozygote for rs3798220, and 6 patients had compounds for both risk alleles (4.4%). Fifty-three patients without risk alleles in their genotype had a mean Lp(a) of 3.48±1.42 μmol·L^{-1}/97.5±39.7 mg·dL^{-1}, 84 patients with at least 1 risk allele had a mean Lp(a) of 4.12±1.74 μmol·L^{-1}/115.3±48.7 mg·dL^{-1}. The difference was marginally statistically different (P=0.046). There seemed to be no distinctive association of both genetic variants with plasma Lp(a) in this population, because Lp(a) strongly exceeded the normal range in both groups. No correlation was found between positive family history for early CAD in first-degree relatives and genotypes. Also, no correlation was found between MACE or ACVE patterns before or after commencing chronic LA and genotypes.
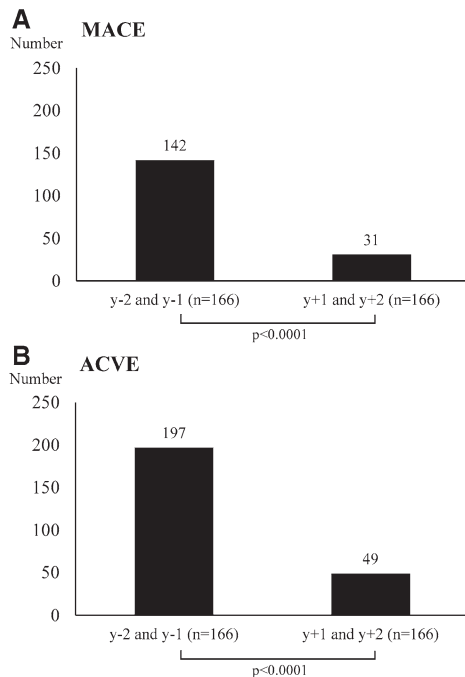

Figure 2. Absolute numbers of MACE (**A**) and ACVE (**B**) in 2 years before (y−2 + y−1) and 2 years after (y+1 + y+2) commencing chronic LA. Depicted *P* values are derived from the analysis of corresponding mean annual rates. ACVE indicates Adverse cardiac or vascular events; LA, lipoprotein apheresis; and MACE, major adverse coronary events.

Figure 3. Absolute numbers of MACE (**A**) and ACVE (**B**) for single years before (y−2, y−1) and after (y+1, y+2) commencing chronic LA. Depicted *P* values are derived from the analysis of corresponding mean annual rates. ACVE indicates Adverse cardiac or vascular events; LA, lipoprotein apheresis; and MACE, major adverse coronary events.
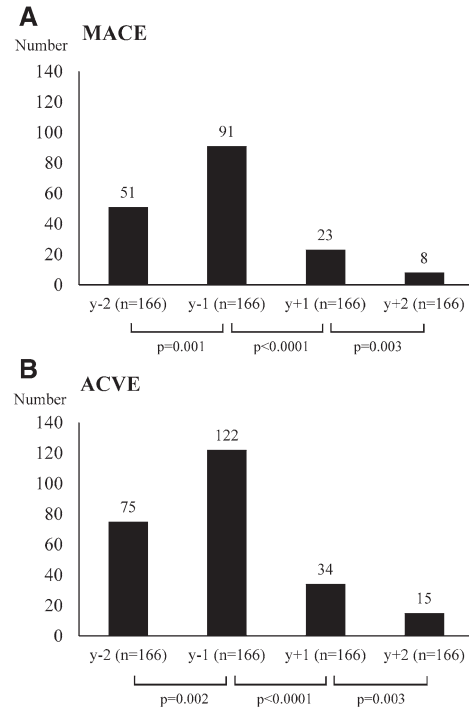
Discussion

In this study, we assessed the incidence of cardiovascular events in patients with Lp(a)-HLP and progressive CVD before and after commencing chronic LA. Elevated baseline levels of Lp(a) were reduced ≈70% immediately after LA sessions. During steady state of chronic LA, Lp(a) showed a rebound before the next treatment to ≈80% of baseline levels (Table 2). Sawtooth-like changes in lipoprotein concentrations are one of the most striking differences between patients undergoing repetitive LA and conventional drug therapy. Differences of mean annual rates for MACE and ACVE comparing prespecified 2-year intervals before LA and during chronic LA were statistically significant and clinically relevant (Tables 5 and 6). Owing to the identical observation periods for all patients, the mean rates directly correspond to differences in absolute numbers of events. In total, 142 MACE before LA versus 31 MACE during LA could be translated into a number needed to treat of 3 to prevent 1 MACE per patient per year. Analysis of mean annual event rates showed a significant increase for MACE and for ACVE between y-2 and y-1, reflecting accelerated progression of CVD. Y+1 after commencing chronic LA was characterized by a remarkable reduction of MACE and ACVE rates in comparison with y-1. Also individual components of MACE, ie, myocardial infarction, percutaneous coronary intervention, and coronary artery bypass graft followed this pattern (Figure 4). Significant decline of mean event rates of MACE and ACVE continued from y+1 to y+2. Internal validity of this pattern is high, because the probability of bias related to missing events is higher in the retrospective

Table 6.   Annual rates for MACE, ACVE, MI, PCI, and CABG for Single Years Before (y-2, y-1) and After (y+1, y+2) Commencing Chronic LA and Percentage Changes (Δ) Between Single Years

	y-2	y-1	y+1	y+2	Δ[y-2/y-1], %	P[y-2/y-1]	Δ[y-1/y+1], %	P[y-1/y+1]	Δ[y+1/y+2], %	P[y+1/y+2]
MACE	0.30±0.58	0.54±0.70	0.14±0.34	0.05±0.21	+80.0	0.001	−74.1	<0.0001	−64.3	0.003
ACVE	0.44±0.73	0.72±0.82	0.20±0.46	0.09±0.31	+63.6	0.002	−72.2	<0.0001	−55.0	0.003
MI	0.13±0.35	0.15±0.36	0.03±0.17	0.01±0.11	+15.4	0.564	−80.0	<0.0001	−66.7	0.257
PCI	0.15±0.40	0.31±0.56	0.09±0.29	0.04±0.19	+106.7	0.003	−71.0	<0.0001	−55.6	0.012
CABG	0.02±0.15	0.08±0.27	0.01±0.11	0	+300.0	0.029	−87.5	0.005	−100.0	0.157

ACVE indicates adverse cardiac or vascular events; CABG, coronary artery bypass graft; LA, lipoprotein apheresis; MACE, major adverse coronary events; MI, myocardial infarction; and PCI, percutaneous coronary intervention.

part of the study. Only 1 cardiovascular death occurred during the first 2 years of LA. An important strength of this study is the prospective analysis of incidence rates of cardiovascular events during chronic LA with a prespecified uniform observation period and a larger number of patients with lower baseline LDL-C in comparison with the first longitudinal cohort study in this field.[10] Completeness and validity of data have been stringently controlled to avoid any selection bias facing the lack of a control group.

LPA risk alleles rs3798220 or rs10455872 were enriched in this study population. At least 1 risk allele was detected in 61.3%, in comparison with only 9.0% and 20.6% in PROCARDIS and the Heart Protection Study.[6,14] There was no difference in event rates between risk allele carriers and those without risk alleles. The difference between Lp(a) concentrations of patients with and without risk alleles was not clinically relevant. Positive family history of CVD was not correlated to risk alleles. Thus, there appear to be other unknown genetic, epigenetic, or nongenetic factors increasing Lp(a) levels.

The current understanding of the pathophysiology underlying atherosclerosis suggests a complex multifactorial mechanism that is only partially modulated by LDL-C. The results of this study support the hypothesis that Lp(a) might be a causal factor for precipitating mechanisms of cardiovascular events in patients receiving intensive treatment of their cardiovascular risk factors but still experiencing substantial cardiovascular morbidity. Chronic LA with extracorporeal elimination

of Lp(a) effectively stabilized this course. It seems unlikely that observed significant changes of event rates would have occurred under best medical care alone. However, only a randomized, controlled trial could finally prove this conclusion. Although such a trial of LA has so far been considered unethical, it might become feasible with novel medicines specifically lowering Lp(a). Nicotinic acid is the only agent that has shown a Lp(a)-lowering effect by up to 25% to 40% in clinical practice.[3] The last available galenic retard preparation of nicotinic acid was withdrawn from the European market by the manufacturer in January 2013. Mipomersen, an antisense oligonucleotide controlling biosynthesis of apolipoprotein B present on Lp(a), failed to achieve European approval. PCSK9 inhibitory antibodies lowering LDL-C and, to a certain extent, Lp(a) are still in an investigational stage. LA can be regarded as a reasonable and available therapeutic option for high-risk patients with Lp(a)-HLP and progressive CVD.

Limitations

The results of this study cannot exclude that Lp(a) elevation in this context is only a marker identifying patients at high CVD risk, and that there is no direct causal relationship of Lp(a) elimination by LA and observed reduction of cardiovascular events. There are still many unknowns regarding basic Lp(a) biology and pathobiology, such as the uncertainties regarding the regulation of plasma Lp(a) levels, including posttranslational modifications. Results allow no conclusion about whether LA, in
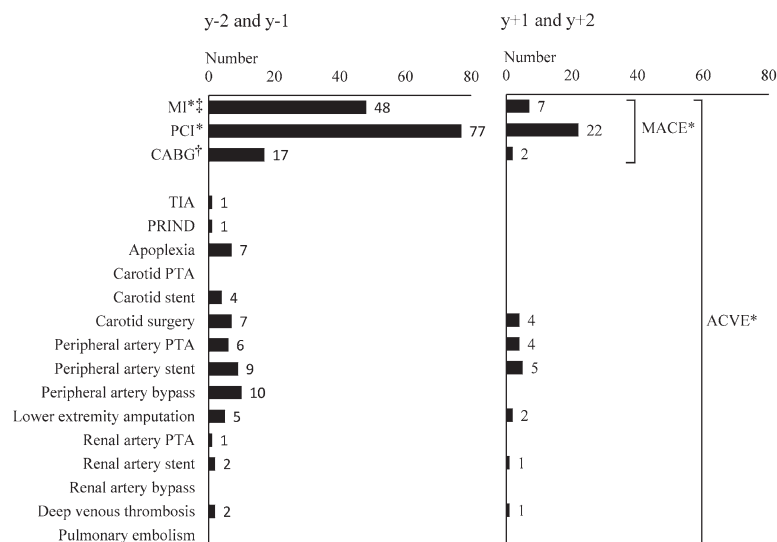

Figure 4. Incidence of events by type and total number in 2 years before (y−2 + y−1) and 2 years after (y+1 + y+2) commencing chronic LA; components of MACE and ACVE are indicated by brackets. *P<0.0001; †P=0.001; ‡number of myocardial infarctions included 1 cardiovascular death at the beginning of year +2 in a patient with critical limb ischemia, end-stage renal disease, and subsequent multiorgan failure. ACVE indicates adverse cardiac or vascular events; CABG, coronary artery bypass graft; LA, lipoprotein apheresis; MACE, major adverse coronary events; MI, myocardial infarction; PCI, percutaneous coronary intervention; PRIND, prolonged reversible ischemic neurologic deficit; PTA, percutaneous transluminal angioplasty; and TIA, transient ischemic attack.

Table 7. Distribution of Genetic Variants rs10455872 and rs3798220 in 137 Genotyped Patients, Classified as Homozygous (hom), Heterozygous (het), and Wild Type (wt)

		rs10455872			
		hom	het	wt	total
rs3798220	hom	0	0	0	0
	het	0	6*	30*	36
	wt	3*	45*	53	101
	total	3	51	83	137

Values indicate absolute numbers (percentages) or mean±SD. SD indicates standard deviation.

*Individuals exhibited at least 1 risk allele (n=84).

addition to cardiovascular morbidity, reduces cardiovascular mortality in these patients. Mortality data for patients with a risk profile identical to this study are not available. The entry sample necessarily is biased by survival. Completed observation of patients until y+4 will enable the analysis of morbidity and mortality over a period of 4 years with chronic LA. All LA methods eliminated LDL-C and Lp(a) with essentially identical efficacy. Therefore, the therapeutic effect is related to the elimination of Lp(a), LDL-C, or both lipoproteins. Also, coelimination of oxidized phospholipids and Lp(a)-PLA2 associated with LDL particles, reduction of triglycerides, and reduction of plasma viscosity may potentially contribute to the overall therapeutic effects seen in this study.

Conclusions

The results of this prospective study support the hypothesis that Lp(a) can be a causal factor for persisting progression of CVD in patients with Lp(a)-HLP when other concomitant cardiovascular risk factors have been intensively treated. Commencing chronic LA could reduce recurrent cardiovascular events at least over a period of 2 years. Assessment of cardiovascular risk in particular for patients who are already at high risk because of established CVD should include the measurement of Lp(a). Epidemiological research is warranted for better understanding of the natural clinical course of these patients, in particular, regarding mortality.

Appendix

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CLINICAL PERSPECTIVE

Evidence from prospective epidemiological studies has accumulated to firmly document an association of elevated circulating levels of lipoprotein(a) (Lp(a)) with cardiovascular disease (CVD) including coronary artery disease, cerebrovascular disease, and peripheral artery disease. Lipoprotein apheresis can lower low-density lipoprotein cholesterol and Lp(a) and is the final escalating option in severely hypercholesterolemic patients, including genetic or other forms of hypercholesterolemia resistant to or intolerant of the use of statins or combined lipid-lowering medication. The major effect of lipoprotein apheresis is the prevention of cardiovascular events. The Pro(a)LiFe study showed that commencing chronic lipoprotein apheresis could reduce the incidence rate of cardiovascular events in patients with Lp(a)-hyperlipoproteinemia and progressive CVD that persisted despite the maximal treatment of other concomitant cardiovascular risk factors. Results of this prospective study support the hypothesis that Lp(a) might be a causal factor for progression of CVD in patients with Lp(a)-hyperlipoproteinemia. Efforts must be made to identify these patients to optimize their treatment including multimodality approaches. The assessment of cardiovascular risk, in particular, for patients who are already at high risk owing to established CVD should include measurement of Lp(a). Lp(a) levels are generally not influenced by lifestyle. A widely useable substance for effective pharmacological lowering of Lp(a) is not yet available. Nicotinic acid at high doses has shown a Lp(a)-lowering effect in clinical practice. Limited by side effects, the use of nicotinic acid has not seen wide application. In Europe, nicotinic acid is no longer available. Lipoprotein apheresis can be regarded as a reasonable and available therapeutic option for high-risk patients with Lp(a)-hyperlipoproteinemia and progressive CVD.