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Longitudinal cohort study on the effectiveness of lipid apheresis treatment to reduce high lipoprotein(a) levels and prevent major adverse coronary events

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SUMMARY

Background We investigated in a longitudinal, multicenter, cohort study whether combined lipid apheresis and lipid-lowering medication can reduce extremely high levels of lipoprotein(a) (Lp[a]) and thus prevent major adverse coronary events (MACE) more efficaciously than lipid-lowering medication alone.

Methods Eligible patients had coronary artery disease and Lp(a) levels ≥2.14 µmol/l (95th percentile). All patients received lipid-lowering medications alone until maximally tolerated doses were no longer effective, followed by combined lipid apheresis and lipid-lowering medication. The rates of the primary outcome, MACE, were recorded for both periods.

Results A total of 120 patients were included. The mean duration of lipid-lowering therapy alone was 5.6 ± 5.8 years, and that of apheresis was 5.0 ± 3.6 years. Median Lp(a) concentration was reduced from 4.00 µmol/l to 1.07 µmol/l with apheresis treatment ($P<0.0001$); the corresponding mean annual MACE rate per patient was 1.056 versus 0.144 ($P<0.0001$).

Conclusions Lowering of Lp(a) levels by apheresis was efficacious and safe, and we recommend this therapy for patients in whom maximally tolerated doses of medication alone have failed to control coronary artery disease-associated events.

KEYWORDS atherothrombosis, lipid apheresis, lipoprotein(a), myocardial infarction, MACE

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Received 4 June 2008 **Accepted** 12 December 2008
www.nature.com/clinicalpractice
doi:10.1038/ncpcardio1456

INTRODUCTION

Lipoprotein(a) (Lp[a]) is a macromolecular complex assembled from apolipoprotein A and LDL. Lp(a) also acts as a structurally homologous competitor of plasminogen and is thought, therefore, to have both atherogenic and prothrombotic potential. Since the discovery of this lipoprotein in the 1960s by Berg,[1] several studies have shown an association between elevated Lp(a) levels and recurrent atherothrombotic complications,[2–12] particularly myocardial infarction (MI)[6,7] and stroke in young and middle-aged individuals,[13] peripheral artery disease,[14] and progression of coronary artery disease (CAD) caused by raised LDL cholesterol levels.[15] By contrast, however, other reports have described Lp(a) as a marker of longevity[16] or as a risk factor that becomes negligible once LDL cholesterol levels are effectively lowered to recommended target levels (≤2.59 mmol/l [i.e. ≤100 mg/dl]).[17–19] Moreover, Lp(a) exists in more than 30 isoforms that have variability in number of kringle 4 repeats[20]; small isoforms are associated with increased risk of CAD and MI in some populations but not in others.[21] Interpretation of the predictive value of Lp(a) has been further complicated by the lack of standardization of Lp(a) measurement[22] and by the fact that routinely applied assays to test LDL cholesterol levels frequently indicate falsely high levels in the presence of elevated Lp(a) concentrations that affect estimation of true risk.[23,24]

In clinical practice, the contradictory reports have affected physicians' decisions regarding evaluation of risk and treatment of individuals with excessively elevated Lp(a) levels. Several studies have demonstrated that extremely high Lp(a) concentrations (>90th percentile) are associated with a more than doubled risk of MI in men and women and with a 10 year MI risk of more than 20% when coupled with hypertension, smoking, or hypercholesterolemia.[3,4,11,25] These large epidemiological studies also confirmed that

Lp(a) values in the 90th percentile or higher are found in 10% of the general population.

Medications such as nicotinic acid,[26] nateglinide,[27] and estrogens for hormone replacement[28] can reduce Lp(a) levels, but only by 10–30%. Lipid apheresis can reduce extremely high Lp(a) levels much further. Successful outcomes with this method have been reported for cases of familial hypercholesterolemia and advanced stages of CAD and transplant arteriosclerosis, and prevention of restenosis after percutaneous coronary intervention (PCI) has also been reported.[29–31] Most apheresis procedures are not, however, specific for Lp(a) removal; they remove both Lp(a) and LDL particles with similar controlled efficacy.

We performed a longitudinal, controlled, multicenter cohort study to investigate whether drastic Lp(a) reduction by means of apheresis treatment, used as a last-resort therapy, would lessen the rate of major adverse coronary events (MACE) in patients with extremely high Lp(a) levels, compared with lipid-lowering medication alone.

METHODS

Study design

In Germany, apheresis can be used only as a last-resort therapy, when all other treatments have been proved unsuccessful, in patients with familial hypercholesterolemia or rapidly progressing CAD with LDL cholesterol and/or Lp(a) elevations far above target levels. Permission is granted on the basis of meticulous and continuous documentation of outcomes and complications and annual external expert lipidologic and cardiologic examinations before the beginning and throughout the duration of therapy. No ethics approval was sought for this study because all potential participants identified by their physicians had already been referred to their respective apheresis center and had at least 3 months of apheresis treatment; their inclusion in the study did not affect the participants' treatment regimens, which were prescribed according to the reimbursement guidelines of the German Federal Joint Committee.[32] All data from before the patient's enrollment in the study (i.e. during their treatment with lipid-lowering medication alone and at least 3 months of apheresis treatment) were analyzed retrospectively. Prospective analysis was performed for any data acquired after enrollment.

Patients

The lead investigator (BRJ) contacted 84 German apheresis centers in December 2004 and asked their physicians to invite all patients with Lp(a) concentration above twice the upper limit of normal (≥2.14 μmol/l) before the initiation of apheresis, who were being treated with apheresis between December 2004 and December 2005, to participate in the study. Of the apheresis centers approached, 27 treated patients with Lp(a) levels above 2.14 μmol/l; all of the patients who met this specification volunteered to participate and signed an informed consent form. Patients were included in the study if they met the following conditions: (a) Lp(a) concentration at the initiation of apheresis above ≥2.14 μmol/l; (b) more than 50% vessel narrowing on angiography and/or a history of MI; and (c) available documentation of maximum tolerated dose of lipid-lowering therapy, including medication and apheresis treatment for at least 3 months, prescribed according to the reimbursement guidelines of the German Federal Joint Committee.[32] Patients with proven familial hypercholesterolemia were excluded because this disease is known to have a distinctly different molecular pathology. Patients with extracardiac manifestation of atherosclerotic disease were also excluded from the study because they did not meet the inclusion criteria.

Medications

Established risk factors were treated according to the American College of Cardiology/American Heart Association guidelines[34] in all patients throughout the study. Patients received antihypertensive medication, antiplatelet therapy, and combined antiplatelet therapy and phenprocoumon for atrial fibrillation or thrombosis. Basic lipid-lowering medication mostly consisted of combination therapy of statins with ezetimibe, nicotinic acid, fibrates, colestyramine, or omega-3 fatty acids; regimens were adapted over the study period as increasingly potent drugs became available. All patients continued taking lipid-lowering medication at maximally tolerated doses during apheresis treatment.

Lipid apheresis

Study participants underwent apheresis every week, 2 weeks, or 10 days for a minimum of 3 months. Details of the lipid apheresis procedures—extracorporeal blood purification to eliminate LDL cholesterol and Lp(a) from plasma through binding of apoprotein B—have been described elsewhere.[36] Briefly, the following methods and devices were used: heparin-mediated LDL precipitation (HELP system® for Plasmat®

Futura; B Braun AG, Melsungen, Germany), whole-blood (DALI; Fresenius SE, Bad Homberg, Germany), dextran-sulfate (LIPOSORBER® system; Kaneka, Osaka, Japan), double filtration plasmapheresis systems (OctoNova®; Diamed, Cologne, Germany, and Plasmaflo® Rheofilter®, Asahi Kasei Kuraray Medical Co., Ltd. Japan), or immune adsorption (Plasmaselect/Terasorb; Miltenyi Biotec GmbH, Bergisch Gladbach, Germany, and Excorim®; Excorim KB Corp, Lund, Sweden) by use of antibody columns directed against the protein part of Lp(a).

Data collection

The cutoff date for data collection was December 2005. The primary outcome was MACE, which comprised MI, the need for PCI and/or CABG, and cardiac death. Secondary outcomes were non-cardiac mortality, reduction of Lp(a), and long-term tolerability of lipid-lowering interventions. A standard questionnaire was used in all apheresis centers to gather information on these outcomes as well as traditional risk factors, family history, cerebral or peripheral artery disease, medication and doses, and laboratory data. Available hospital records were also obtained and assessed as confirmatory information.

The study was documented according to the Ulstein style;[33] data were entered into a database by one investigator, and cross-checked twice each by two independent investigators who were unaware of patients' identities and histories.

Lipoprotein profiles were established and monitored by measurement of total cholesterol, non-fasting triglycerides, LDL cholesterol (measured directly rather than calculated), HDL cholesterol and Lp(a) concentrations; levels of fibrinogen were also monitored. Creatinine and C-reactive protein were measured at baseline only. Corrected LDL cholesterol levels were also calculated because around 45% of the Lp(a) particle is falsely added to LDL cholesterol in almost all routinely used LDL assays.[23,24] All apheresis centers used the same assays before and after initiation of the apheresis treatment regimen. During apheresis treatment, laboratory variables were measured 30 minutes after the end of the apheresis session, when the reduction in lipid levels is greatest. Laboratory values are known to rise between apheresis sessions and, therefore, we also provide mean interval values obtained between apheresis treatments.

Accuracy of extremely elevated Lp(a) levels measured in the respective centers was assessed by cross-checking of a randomly selected subset of lipoprotein profiles for 45 patients by the Institute of Clinical Chemistry, LMU University Munich, Germany, where a patented lyophilized Lp(a) standard was developed.[35]

Statistical analysis

The primary objective was to compare the annual MACE rate arising with lipid-lowering medication only versus that arising with medication plus apheresis in the same individuals. The time periods for each treatment differed between patients and, therefore, the annual MACE rate per patient was calculated by dividing individual MACE rate during the period of lipid-lowering medication alone and during the apheresis treatment period by the individual's observation times. Annual rates for the individual components of MI, CABG, PCI, and cardiac death were similarly calculated. If a patient experienced MACE more than once within 1 day, only the triggering event was counted; if patients experienced repeated occurrences of individual components of MACE on different days, all events were considered.

Differences between the two treatment periods were calculated with a two-sided Wilcoxon matched-pairs signed-rank test ($\alpha < 0.05$).

We also used the Kruskal-Wallis test to investigate whether the apheresis techniques differed in efficacy with regard to the reduction of MACE rate. This analysis also allowed us to indirectly assess the potential impact of the concomitant partial elimination of other risk factors, such as fibrinogen and C-reactive protein, which occurred with two of the devices, namely the heparin-mediated LDL precipitation and the double filtration plasmapheresis systems.

We performed two subgroup analyses in the study. First, we investigated the effect of LDL cholesterol lowering on MACE outcomes, since lowering of LDL cholesterol is purported to negate the effect of lowering Lp(a). To assess this difference, we stratified the cohort into patients whose LDL cholesterol levels reached less than 2.59 mmol/l during lipid-lowering medication alone and those who did not. Second, we assessed differences in MACE rates between patients who withdrew from apheresis and those who continued until the end of the study.

RESULTS

Patients' characteristics

Of the 144 patients who volunteered for the study after being identified by apheresis center

Table 1 Patient baseline characteristics.

Characteristic	Patients (%) [*n* = 120] or value
Anthropometric	
Male	86 (71.7)
Mean (±SD) age at CAD diagnosis (years)	48.8 ± 11.0
Mean (±SD) age at initiation of apheresis (years)	54.4 ± 10.6
Mean (±SD) BMI (kg/m2)	26.7 ± 3.5
Clinical	
Positive family history for CAD[a]	92 (76.7)
Current smokers	2 (1.7)
Former smokers[b]	58 (48.3)
Never smoked	60 (50.0)
Diabetes mellitus[c]	19 (15.8)
Type 1 diabetes	17 (14.2)
Type 2 diabetes	2 (1.7)
Hyperfibrinogenemia (>13.2 µmol/l)	16 (13.3)
Elevated C-reactive protein (>1.0 mg/dl)[d]	20 (22.7)
Elevated creatinine levels (>106 µ mol/l)[e]	16 (13.3)
Terminal kidney failure	4 (3.3)
Renal artery stenosis	5 (4.2)
Cerebral atherosclerosis	66 (55.0)
Peripheral atherosclerosis	32 (26.7)

[a]A positive family history for CAD or stroke in first-degree relatives before age 65 years. [b]Of the former smokers, the majority (82.3%) quit smoking before or at the time of CAD diagnosis, 11.7% quit during lipid-lowering medication alone, and 6.0% quit at or after the onset of apheresis. [c]Of the patients with diabetes mellitus, 15 patients were receiving insulin in addition to oral medication. [d]Plasma C-reactive protein concentration before apheresis was available in 88 patients; the mean level was 1.2 ± 2.2 mg/dl. [e]Mean serum creatinine concentration was 97.2 ± 53.0 µmol/l.

physicians as having high Lp(a) concentrations, 7 were excluded because of familial hypercholesterolemia and 17 were excluded because they had atherosclerotic disease without CAD; therefore, 120 patients that met the inclusion criteria were included in the study. Table 1 shows the patients' clinical characteristics at baseline (before apheresis). The mean age at which CAD was first diagnosed was 48.8 (±11, range 16–73) years in the 120 recruited patients. A significant number of patients had concomitant cerebral (55%) and/or peripheral (26.7%) atherosclerosis. The percentage of former smokers was high (48.3%) compared with that in the total German population (18.9%).[37]

Mean overall follow-up duration was 10.9 ± 6.6 years, with the mean duration of treatment with lipid-lowering medication only being 5.5 ± 5.8 years and time from start of apheresis to end of follow-up being 5.0 ± 3.6 years. Apheresis was performed weekly in 94 individuals, fortnightly in 24 participants, and every 10 days in 2 patients. Characteristics of therapy are shown in Table 2.

Laboratory findings before and after intervention

Laboratory findings before apheresis (i.e. during lipid-lowering medication alone) and during apheresis are shown in Table 3. Lp(a) levels were substantially elevated, compared with normal reference ranges, when patients were taking maximal lipid-lowering medication; the median concentration of Lp(a) before apheresis treatment was 4.00 µmol/l (i.e. 112 mg/dl). By contrast, total cholesterol, nonfasting triglycerides, HDL cholesterol, C-reactive protein and fibrinogen levels were within, or only slightly above, reference ranges, indicating that these risk factors were adequately controlled by standard medication. The mean LDL cholesterol level was still above the target value despite maximal lipid-lowering medication.

Apheresis reduced the median Lp(a) levels (trough concentrations) by 73% compared with those during lipid-lowering medication alone (i.e. to 1.07 µmol/l [30 mg/dl]) and substantially lowered all other laboratory values (all $P<0.0001$; Table 3). The reduction of nonfasting triglycerides achieved by apheresis was not enduring because of quick synthesis rates. Reductions in fibrinogen and C-reactive protein had no significant effect on MACE reduction in this cohort.

Major adverse coronary events

The incidence of MACE, particularly PCI, increased exponentially during the period of lipid-lowering medication alone, despite maximally tolerated doses being administered (Figure 1). During this period, the overall annual MACE rate was 1.056 MACE per patient. The annual complication rate during apheresis was 0.144 MACE per patient; therefore, the observed apheresis-associated risk reduction for all MACE was 86% ($P<0.0001$, Figure 2).

Of the MACE that occurred during the apheresis treatment period, 40% occurred in the first year, and of these, 77% of events occurred in the first 6 months. The MACE rate subsequently declined (Figure 1). No differences in MACE reduction were found among the different lipid apheresis devices used.

Before apheresis, MI was recorded 89 times in 68 patients, PCI 146 times in 69 patients, and CABG 62 times in 57 patients, yielding a total of

297 MACE in 103 patients. During apheresis, the complication rate decreased to 57 MACE in 29 patients, comprising 7 MI in 6 patients, 36 PCI in 19 patients and 14 CABG in 12 patients (Figure 1). The youngest study participant was 16 years old when he experienced the first of three MIs; he began apheresis at age 33 and has been event free for 6 years. Of the patients who underwent CABG, 18% had repeat surgery at least once (one patient underwent three operations). Also, several patients had exaggerated thrombus formation shortly after PCI; the worst case was one patient who had to undergo PCI reintervention five times within 1 week.

Analysis of the individual components (Figure 2) revealed that the annual MI rate decreased from 0.374 to 0.011 (97%, $P<0.0001$), the annual PCI rate from 0.797 to 0.069 (91%, $P<0.0001$) and the annual rate of CABG operations from 0.179 to 0.020 (89%, $P<0.0001$).

All patients included in the study had to be alive until at least the third month of apheresis treatment to enable comparison of data before and during apheresis. Because of this inclusion criterion, mortality during the period patients were receiving lipid-lowering medication alone was zero. Death rate during the apheresis period was one death per 261 patient years, and was counted as part of the MACE. In total, five patients died of cardiac complications: three sudden cardiac deaths, one fatal MI, and one fatal cardioembolic stroke. These five patients had severe long-term cardiac histories with unfavorable comorbidities, including long-term terminal renal failure, end-stage diabetic complications such as limb amputation, severe ischemic cardiomyopathy, recurrent pulmonary embolism, and complicated surgery for severe aortic valve stenosis. Three of the five patients died within the first year of apheresis treatment. No further reasons of death were identified, and no associations were found between the cause or time of death and apheresis treatment itself.

Table 2 Patient treatment characteristics.

Therapy	Patients ($n=120$)
Antihypertensive medication[a]	**84 (70.0%)**
β-Blockers[b]	95 (79.2%)
Diuretics	54 (45.0%)
Angiotensin II type I receptor antagonists	48 (40.0%)
Angiotensin-converting enzyme inhibitors	22 (18.3%)
Nitrates	26 (21.7%)
Calcium channel blockers	24 (20.0%)
Antiplatelet medication	**120 (100.0%)**
100 mg Acetylsalicylic acid/day	88 (73.3%)
75 mg Clopidogrel/day	36 (30.0%)
100 mg Acetylsalicylic acid and 75 mg clopidogrel/day	23 (19.2%)
Phenprocoumon[c]	13 (10.8%)
Lipid-lowering medication	**120 (100.0%)**
Statins[d]	114 (95.0%)
Ezetimibe	50 (41.7%)
Nicotinic acid	10 (8.3%)
Fibrates	7 (5.8%)
Cholestyramine	4 (3.3%)
Omega-3 fatty acids	4 (3.3%)
Apheresis[e]	**120 (100%)**
Heparin-mediated LDL precipitation	56 (39.7%)
Whole-blood adsorption	33 (23.4%)
Double filtration plasmapheresis	24 (17.0%)
Dextran sulfate adsorption	19 (13.5%)
Immune adsorption	9 (6.4%)

[a]Antihypertensive therapy was given to 70% of the patients to treat arterial hypertension. [b]In some cases, β-blockers were prescribed for reasons other than antihypertensive care (e.g. as antiarrythmics). [c]Combined with antiplatelet therapy for atrial fibrillation or thrombosis. [d]Including 40–80 mg atorvastatin daily, 40–80 mg simvastatin daily, and 80 mg fluvastatin daily. [e]The values for the individual types of apheresis add up to more than 120 (100%), since patients swapped method according to need.

Effect of withdrawal from apheresis

Withdrawal from apheresis or long interruption to apheresis treatment was necessary for 17 patients because reimbursement was cancelled. For these patients, we analyzed complication rates before and during apheresis and after withdrawal. The mean duration of receiving lipid-lowering medication alone was 4.3 (±3.5) years, during which the annual complication rate was 1.07 per patient. The mean duration of apheresis was 4.3 (±3.7) years, during which the annual MACE rate fell to 0.04 per patient. During the withdrawal period to the end of follow-up or until reinitiation of apheresis (1.9 [±1.3] years), the annual complication rate increased to 0.13 per patient, including six cardiac interventions in four patients and one fatal MI. These data show a clear worsening trend, although statistical analyses were not performed because of the small numbers.

Effects of LDL cholesterol lowering

In the stratified analysis, LDL cholesterol levels of 2.59 mmol/l (i.e. 100 mg/dl) or lower were achieved

Table 3 Laboratory values before and during apheresis treatment.

Laboratory variable	Target level	Mean (±SD) concentration		
		Before apheresis[a]	During apheresis	
			Trough concentration[b]	Interval concentration[c]
Lipoprotein(a) (μmol/l)[d]	<1.07	4.21 ± 1.50	1.18 ± 0.57	2.68 ± 0.89
Total cholesterol (mmol/l)[e]	<5.18	5.67 ± 1.86	2.64 ± 0.75	4.12 ± 1.19
LDL cholesterol (mmol/l)[e]	<2.59	3.26 ± 1.27	1.17 ± 0.60	2.20 ± 0.85
HDL cholesterol (mmol/l)[e]	>1.04	1.40 ± 0.44	1.19 ± 0.36	1.35 ± 0.39
Triglycerides (mmol/l)[f]	<2.03	2.05 ± 1.31	0.97 ± 0.63	1.47 ± 0.86
Fibrinogen (μmol/l)[g]	<8.82	9.58 ± 2.82	5.85 ± 2.88	8.47 ± 2.44

P <0.0001 for all comparisons. [a]Measured during therapy with maximally tolerated lipid-lowering medication. [b]Samples were taken around 30 min after the end of apheresis. [c]The average reduction achieved in the interval between two apheresis sessions. [d]To convert to mg/dl divide by 0.0357. [e]To convert to mg/dl divide by 0.0259. [f]To convert to mg/dl divide by 0.0113. Values were available for only 95 patients. [g]To convert to mg/dl divide by 0.0294. Values were available for only 88 patients.

with lipid-lowering medication alone in 42 of 120 patients. The mean LDL cholesterol concentration among these patients was 1.97 ± 0.44 mmol/l, compared with 3.96 ± 0.96 mmol/l among patients whose levels did not fall below this threshold. The levels of Lp(a) were similar in the two subgroups, as were levels of HDL cholesterol, triglycerides, and fibrinogen (Table 4). When measured LDL cholesterol levels were corrected for cholesterol derived from Lp(a), the LDL cholesterol concentrations before and during apheresis were only 0.60 mmol/l and 0.47 mmol/l, respectively, in patients who achieved uncorrected LDL cholesterol concentrations lower than 2.59 mmol/l with lipid-lowering medication alone. The corrected values were 2.56 mmol/l and 0.98 mmol/l, respectively, in those who did not. The MACE rates before and during apheresis treatment did not differ significantly between these subgroups (Table 5), indicating that the reduction of LDL cholesterol levels had little impact on the reduction of MACE.

Long-term tolerability of lipid-lowering medication and lipid apheresis

During the period of analysis, 15% of patients had to stop statin therapy because of myopathy and an additional 3% of patients switched to another statin because of intolerance to the medication. Of the 50 patients taking ezetimibe, 5% reported gastrointestinal problems or myopathy. No cases of rhabdomyolysis occurred.

Adherence to apheresis treatment with intervals of 1 week, 2 weeks, or 10 days was excellent (100%). No major adverse effects were observed in any schedule. Minor complications at the site of venipuncture, transient hypotension, muscle cramps, and fatigue after treatment occurred in less than 5% of patients and were mostly related to the extracorporeal procedure, rather than to a specific device.

DISCUSSION

Given the hypothesis that extremely high Lp(a) concentrations play a crucial role in atherothrombosis, lowering levels should reduce the risk of atherothrombotic complications. Our findings suggest that lipid apheresis in these patients achieves near-normal Lp(a) levels and prevents MACE. These effects were seen across all 27 participating centers. The efficacy of apheresis is further supported by the increased age and longer history of MACE at the start of this therapy than at the start of maximally tolerated lipid-lowering medication alone, and by a threefold increase of MACE within 2 years in a subgroup who withdrew from apheresis.

The MACE rate was highest before apheresis despite the patients receiving state-of-the-art lipid-lowering regimens throughout the study, presumably because Lp(a) levels were substantially raised. The decreased MACE rates during apheresis corresponded with dramatic reductions in Lp(a) levels. The results were not confounded by effects of hypertension and diabetes, since treatments were maintained before and during apheresis. Likewise, the timing of smoking cessation did not affect outcomes.

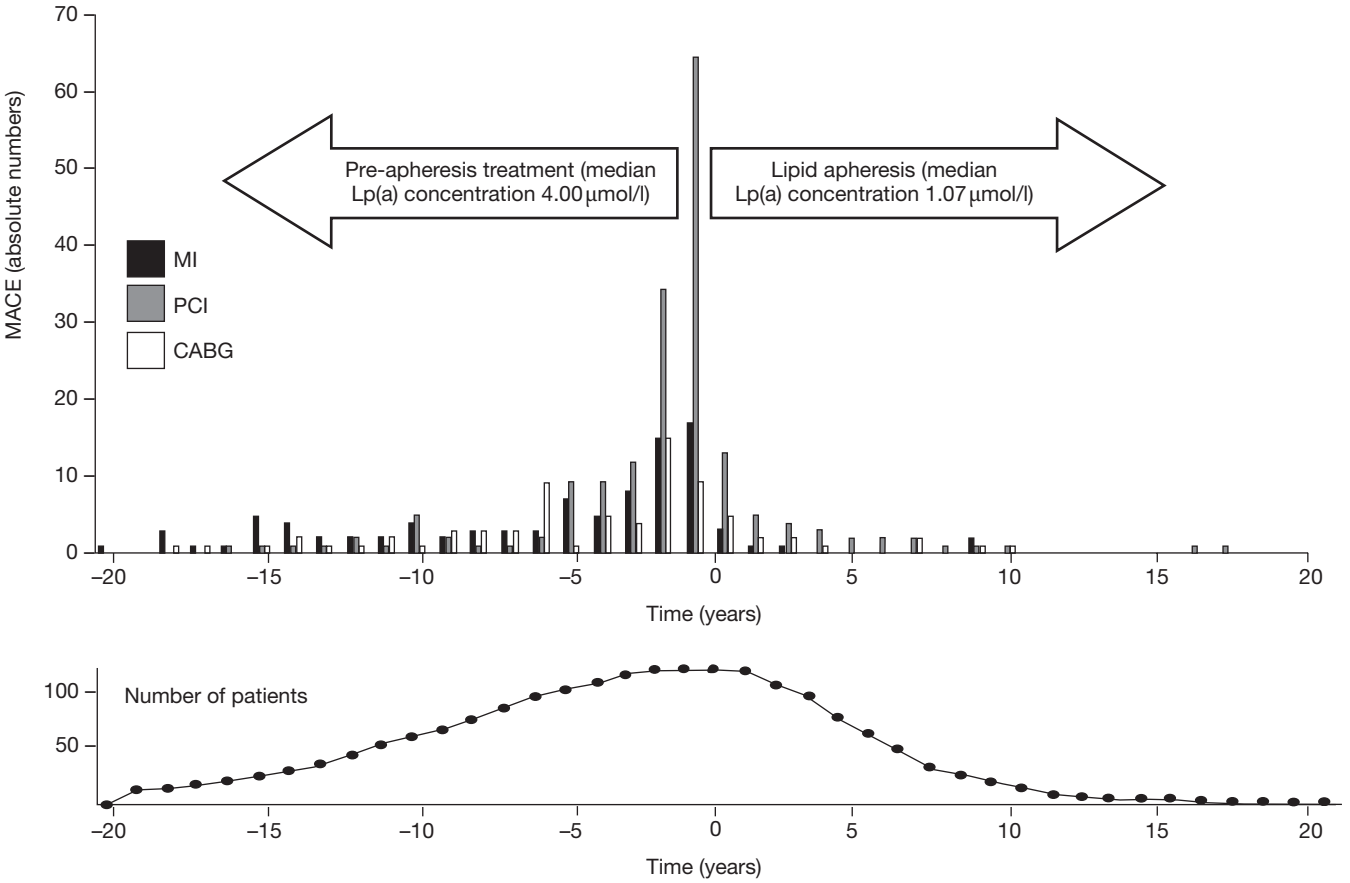

Figure 1 Absolute numbers of major adverse coronary events during lipid-lowering medication alone and during combined lipid-lowering medication and lipid apheresis. Timepoint zero corresponds with the beginning of apheresis treatment for each patient. Since individual observation times varied, the number of patients studied for each year is shown in the lower panel. Abbreviations: CAD, coronary artery disease; Lp(a), lipoprotein(a); MACE, major adverse coronary events; MI, myocardial infarction; PCI, percutaneous coronary intervention.

In support of the relationship between Lp(a) and MACE, the 4S study of patients with coronary heart disease showed that the rate of recurrent MACE doubled, and the statin effect on death reduction was notably decreased, in patients with high Lp(a) levels compared with that in patients with moderate Lp(a) levels.[4] The Copenhagen Study[25] reported a 10 year MI risk of more than 20% in patients with extremely high Lp(a) concentrations and hypertension, history of smoking, or both.

Simultaneously elevated Lp(a) and LDL cholesterol levels multiply the risk of MACE,[2,4,8,11,15,24] and whether clinical improvement achieved with apheresis truly originates from Lp(a) reduction or results from the concomitant reduction of LDL cholesterol and Lp(a) by similar proportions is debated. One idea is that Lp(a) elevations are irrelevant once LDL cholesterol is sufficiently lowered.[17–19] The Familial Hypercholesteroleamia Regression Study (FHRS)[17] and the LDL Apheresis Atherosclerosis Regression Study (LAARS)[18] reported that apheresis significantly reduces levels of LDL cholesterol and Lp(a). In patients whose LDL cholesterol levels were effectively lowered by medication or apheresis, though, reduction of Lp(a) concentrations had no additional effect in improving angiographic features of CAD. Following our subgroup analysis of patients with LDL cholesterol levels less than or greater than 2.59 mmol/l before apheresis, however, we reject the hypothesis. The subgroups differed significantly in concentrations of LDL cholesterol (uncorrected and corrected) and total cholesterol but not in those of Lp(a), HDL cholesterol, triglycerides, or fibrinogen. Given that the subgroups had similar reductions in MACE rate, LDL cholesterol concentration is unlikely to have determined outcome. The findings after

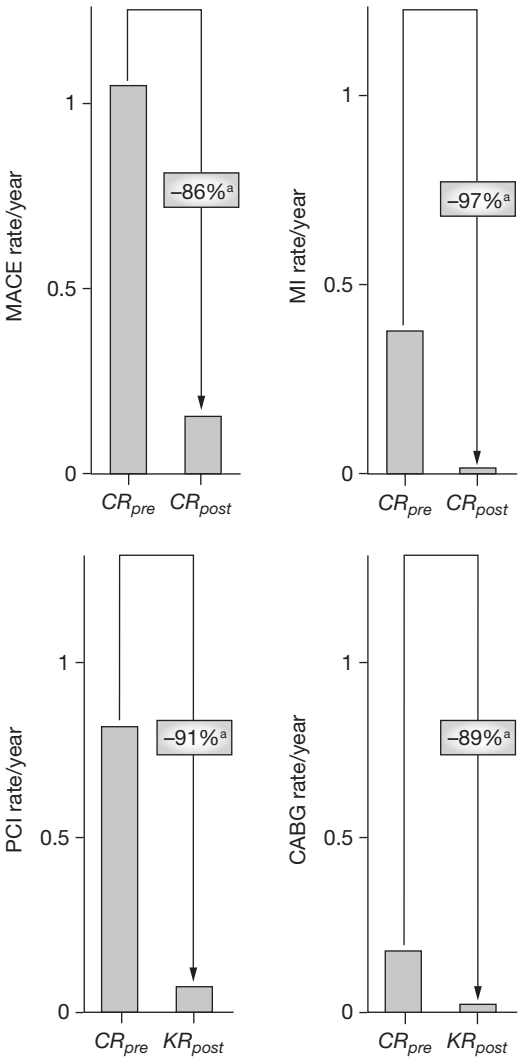

Figure 2 Changes in annual nonfatal MACE rates before and after initiation of lipid apheresis. For calculation of the annual complication rates, when a patient experienced multiple MACE in 1 day only the causative event was counted. The annual complication rates are, therefore, lower than the sum of all single events. [a]$P<0.0001$. Abbreviations: CAD, coronary artery disease; CR_{pre}, complication rate before apheresis; CR_{post}, complication rate after apheresis was started; MACE, major adverse coronary events; MI, myocardial infarction; PCI, percutaneous coronary intervention.

correction of LDL cholesterol strengthen this argument; the reduction in true LDL cholesterol values in patients whose uncorrected LDL cholesterol levels reached 2.59 mmol/l or less was too small to explain the 87% reduction in MACE.

The apparent discrepancy between our results and those of FHRS and LAARS might be related to the facts that these trials assessed angiographic features of CAD and not MACE rates and that they included patients with familial hypercholesterolemia, which has a specific molecular pathology and predominant increases in LDL levels. Thus, the thrombogenic properties of extreme Lp(a) concentrations might be more relevant to cardiovascular complications than to angiographic progression.

In the present study, we observed a substantial proportion of MACE occurring shortly after endothelial injury caused during catheter-based procedures or CABG, particularly before the start of apheresis therapy. Associations between raised Lp(a) concentrations and the recurrence of atherosclerosis after PCI and CABG have been described by others,[4,38,39] and like others before, we propose an underlying prothrombotic effect of Lp(a). In particular, we hypothesize that the missing link may be the injury-mediated release of endothelium-derived factors capable of activating the acute-phase properties of the apoprotein(a) in the Lp(a) particle. In support of this hypothesis, when concentrations of Lp(a) are high, particles have been shown to bind with high affinity at sites of endothelial injury and trigger the release of hemostatic factors, such as tissue factor pathway inhibitor, CD40, fibronectin, platelet-derived growth factor, and platelet-activating factor, which promote thrombus formation.[10–12, 38–40] In this setting, Lp(a) acts as a substrate and effector, and as a catalytic or inhibitory player, because the resolution of thrombus formation is associated with high affinity binding of Lp(a) to factor XIII and fibrin(ogen).[10–12,40] Lp(a) not only is part of early atherosclerotic lesions, but it also exerts effects on platelets, macrophages, adhesion molecules, phospholipids, and extracellular matrix proteoglycans, all of which participate in promoting wound healing. Therefore, invasive procedures that cause endothelial injury are likely more troublesome for patients with high Lp(a) levels, and apheresis might improve the MACE rate because it reduces the overabundance of Lp(a) to levels below that at which the atherothrombotic risks are also reduced.

Three limitations in our study need to be mentioned. First, the study has retrospective and prospective components. We selected this design, however, because it allowed us to carefully select the cohort, generate clear end points, include external quality controls, and build close affiliations with the apheresis centers over the years of follow-up.

Table 4 Laboratory variables before and after intervention for patients stratified by preintervention LDL cholesterol levels.

Mean (±SD) laboratory variable	Lipid-lowering medication only			Apheresis plus lipid-lowering medication		
	LDL cholesterol achieved with lipid-lowering medication alone		*P* value	LDL cholesterol achieved with lipid-lowering medication alone		*P* value
	≤2.59 mmol/l (*n* = 42)	>2.59 mmol/l (*n* = 78)		≤2.59 mmol/l (*n* = 42)	>2.59 mmol/l (*n* = 78)	
Lipoprotein(a) (μmol/l)[a]	4.18 ± 1.21	4.25 ± 1.64	0.779	1.14 ± 0.54	1.21 ± 0.61	0.605
Total cholesterol (mmol/l)[b]	4.40 ± 1.76	6.35 ± 1.55	<0.0001	2.25 ± 0.57	2.85 ± 0.78	<0.0001
LDL cholesterol (mmol/l)[b]	1.97 ± 0.44	3.96 ± 9.58	<0.0001	0.83 ± 0.39	1.37 ± 0.62	<0.0001
Corrected LDL cholesterol (mmol/l)[b]	0.60	2.56	<0.0001	0.47	0.98	<0.0001
HDL cholesterol (mmol/l)[b]	1.37 ± 0.47	1.42 ± 0.44	0.359	1.22 ± 0.36	1.19 ± 0.39	0.727
Triglycerides (mmol/l)[c]	1.89 ± 1.11	2.14 ± 1.40	0.555	0.81 ± 0.46	1.06 ± 0.71	0.104
Fibrinogen (μmol/l)[d]	9.53 ± 3.15	9.61 ± 2.68	0.725	5.70 ± 2.88	5.85 ±2.91	0.799

[a]To convert to mg/dl divide by 0.0357. [b]To convert to mg/dl divide by 0.0259. [c]To convert to mg/dl divide by 0.0113. [d]To convert to mg/dl divde by 0.0294.

Table 5 Annual rates of nonfatal major adverse coronary events stratified by LDL cholesterol levels achieved with lipid-lowering medication alone.

MACE	LDL cholesterol level achieved with lipid-lowering medication alone							
	≤2.59 mmol (i.e. ≤100 mg/dl), *n* = 42				>2.59 mmol/l (i.e. >100 mg/dl), *n* = 78			
	MACE rate during lipid-lowering medication alone	MACE rate during apheresis	Reduction (%)	*P* value	MACE rate during lipid-lowering medication alone	MACE rate during apheresis	Reduction (%)	*P* value
MACE	1.190	0.136	89%	<0.0001	0.984	0.149	85%	<0.0001
MI	0.436	0.008	98%	<0.0001	0.314	0.013	96%	<0.0001
PCI	0.824	0.053	94%	<0.0001	0.783	0.078	90%	<0.0001
CABG	0.259	0.029	89%	0.0021	0.136	0.015	89%	<0.0001

Abbreviations: MACE, major adverse coronary events; MI, myocardial infarction; PCI, percutaneous coronary intervention.

Second, we appreciate that the study lacks a direct standard of comparison between treatments for the mortality analysis, because an inclusion criterion was that the patients survived until apheresis. Statistically, even with an underestimated death rate during the period of lipid-lowering medication alone (which is to the disadvantage of our hypothesis), our results remain significant. Moreover, five deaths (i.e. one per 261 patient years) following initiation of apheresis is a remarkably low rate for a high-risk cohort, particularly given their long histories of heart disease and their unfavorable comorbidity, such as long-term end-stage renal disease, end-stage diabetes, recurrent pulmonary embolism, and severe aortic valve stenosis. Notably, most apheresis-associated MACE occurred during the first 6 months after treatment started and then steadily declined.

Third, it is difficult to prove unambiguously that concomitant reduction of other proatherogenic blood compounds through apheresis was not beneficial. Fibrinogen and C-reactive protein, for example, are reduced by some, but not all, of the applied apheresis devices. Nevertheless, MACE rate reductions were similar for all the applied devices, regardless of whether they lowered fibrinogen and C-reactive protein levels, although the number of patients treated by each were small. In our cohort, changes in concentrations of these risk markers might have a complementary benefit, but limited effects are likely since fibrinogen and C-reactive protein concentrations were already normal or only moderately elevated before the initiation of apheresis.

Lipid apheresis provided a highly efficacious and safe tool to reduce Lp(a) levels, and this

therapy should be considered for treatment of patients in whom maximally tolerated doses of medication alone have failed to control CAD-associated events. Selection of individuals who have early atherosclerosis, or a positive family history for this disease, by screening for elevated Lp(a) levels might be useful to direct management. Study is warranted to distinguish between unhealthy and harmless Lp(a) elevations to develop primary preventive strategies according to individual risks. Finally, despite good adherence to apheresis with intervals of 1 to 2 weeks between sessions, this therapy is an intricate and long-term option. Our findings highlight the need for the development of drugs to effectively lower extremely high Lp(a) concentrations in patients with CAD.

Supplementary information in the form of an appendix is available on the *Nature Clinical Practice Cardiovascular Medicine* website.

KEY POINTS

- The clinical relevance of lipoprotein(a) to atherothrombotic complications has been a matter of diagnostic and therapeutic controversy
- Our findings provide evidence that lowering concentrations of lipoprotein(a) significantly reduces the rate of major adverse coronary events
- Application of lipid apheresis—the only currently available method to drastically reduce lipoprotein(a) levels—safely and efficaciously reduced the frequency of myocardial infarction by 97%, irrespective of LDL cholesterol concentrations before therapy
- Screening for extremely high lipoprotein(a) elevations in patients with premature atherosclerosis, recurrent MACE, or a positive family history for atherosclerosis might be useful to direct therapy
- Given the inconvenience of apheresis therapy, our findings highlight the need for development of drugs to effectively lower pathogenic lipoprotein(a) concentrations

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Acknowledgments
We would like to dedicate this article to Kåre Berg. We are indebted to the patients for their trust and our families for their advice, encouragement and support. We appreciate the dedicated help of the colleagues and nurses of the participating apheresis centers.

Competing interests
The authors declared no competing interests.