Chapitre 9 Des concentrations élevées de triglycérides chez des patients avec hypercholestérolémie familiale homozygote attenuent l'efficacité de l'aphérèse des lipoprotéines avec l'adsorption au sulfate de dextran

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High serum triglyceride concentrations in patients with homozygous familial hypercholesterolemia attenuate the efficacy of lipoprotein apheresis by dextran sulfate adsorption

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Résumé

Contexte et objectif : Maximiser les diminutions dans les concentrations de C-LDL et de Lp(a) est le principal objectif de l'AL dans le traitement de l'HFHo. L'objectif de cette étude était d'examiner comment les concentrations pré-AL de TG influencent l'efficacité de l'AL à induire une baisse aiguë dans les concentrations de C-LDL et de Lp(a) chez des patients avec HFHo.

Méthodes : Les données de 1761 traitements d'AL réalisés entre 2008 et 2016 chez des patients avec HFHo (n=10) et avec HFHe composée (n=5) ont été compilées et analysées. Ces données incluent les concentrations de C-LDL, de TG et de Lp(a) pré- et post-AL, le volume de plasma filtré à chaque traitement, le système utilisé [précipitation extracorporelle des LDL induite par l'héparine (HELP) ou l'adsorption au sulfate de dextran (ASD)] et l'intervalle de temps entre les traitements.

Résultats : Une association significative entre les concentrations de TG pré-AL et la diminution aiguë des niveaux de C-LDL induite par l'AL, modifiée par le système utilisé, a été observée ($P_{\text{quartiles de TGs pré-AL * système d'AL}}$=0,04). En utilisant le système avec l'ASD, la diminution aiguë des concentrations de C-LDL était atténuée de 3,9% quand les concentrations de TG pré-AL étaient > 2,09 mmol/L comparativement aux concentrations ≤ 0,93 mmol/L (quartile supérieur vs quartile inférieur : -59,4% vs -63,3% ; *P*=0,007). En utilisant le système HELP, aucune différence significative n'a été observée dans la réduction des niveaux de C-LDL entre le quartile supérieur et le quartile inférieur des concentrations de TG pré-AL (-65,8% vs -66,4% ; *P*=0,9). Aucune association n'a été observée entre les concentrations de TG pré-AL et la diminution des concentrations de la Lp(a) induite par l'AL.

Conclusions : L'efficacité du système à l'ASD, mais pas celle du système HELP, est inversement associée aux concentrations de TG pré-AL des patients avec HFHo.

Title page

High serum triglyceride concentrations in patients with homozygous familial hypercholesterolemia attenuate the efficacy of lipoprotein apheresis by dextran sulfate adsorption

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Abstract

Background and aims: Maximizing the acute reduction of LDL-cholesterol (C) and lipoprotein (a) (Lp(a)) concentrations in patients with homozygous familial hypercholesterolemia (HoFH) is the main goal of lipoprotein apheresis (LA). The objective was to examine how the pre-LA serum TG concentrations influence the efficacy of LA to acutely reduce LDL-C and Lp(a) concentrations in HoFH patients.

Methods: Data from 1761 LA treatments of HoFH patients (n=10) and compound heterozygous patients (n=5) collected between 2008 and 2016 were analyzed. These data included the pre- and post-LA concentrations of LDL-C, TGs and Lp(a); volume of filtered plasma; type of LA system used (dextran sulfate adsorption (DSA) or heparin-induced extracorporeal LDL precipitation (HELP)); and interval between treatments.

Results: A significant association between the pre-LA TG concentrations and acute LA-induced reduction in LDL-C, modified by the type of LA system used, was observed ($p_{\text{pre-LA TG quartile*LA system}}$=.04). Using the DSA system, the acute reduction of the LDL-C concentrations was attenuated by 3.9% when the pre-LA TG concentrations were >2.09 mmol/L vs. ≤0.93 mmol/L (highest vs. lowest quartiles: -59.4% vs. -63.3%, p=.007). Using the HELP system, no significant difference was observed in the reduction of LDL-C between the highest and the lowest quartiles of serum TGs (-65.8% vs. -66.4%, p=.9). No association was observed between the pre-LA TG concentrations and acute LA-induced decrease in Lp(a) (p=.2).

Conclusions: The efficacy of LA is inversely associated with the pre-LA TG concentrations in HoFH patients that used the DSA system instead of the HELP system.

Keywords Homozygous familial hypercholesterolemia, lipoprotein apheresis, dextran sulfate adsorption, triglyceride, LDL-cholesterol

Introduction

The clinical features of homozygous familial hypercholesterolemia (HoFH), which is caused by mutations in the LDL receptor (*LDLR*) gene, are markedly high LDL-cholesterol (C) concentrations, tendon and skin xanthomas, extensive atherosclerosis and extreme risk of coronary artery disease (CAD).[1] LDLR deficiency is also associated with increased lipoprotein (a) (Lp(a)) concentrations, which also contribute significantly to CAD risk in patients with FH.[2-4] If untreated, patients with HoFH usually develop CAD during childhood or adolescence.[5]

Pharmacological treatment is insufficient to reduce LDL-C or Lp(a) concentrations in HoFH patients, and repetitive long-term lipoprotein apheresis (LA) remains the gold-standard therapy.[6, 7] Bi-monthly LA is effective at reducing the concentrations of atherogenic apolipoprotein (apo) B-containing lipoproteins and increasing the life expectancy of HoFH patients.[8, 9] Achieving the maximum acute reductions in LDL-C and Lp(a) concentrations to reduce the chronic exposure of patients with HoFH to atherogenic particles is the key goal of LA.[10] The method used to remove apoB-containing particles (adsorption, precipitation, or filtration) and the LA system filtration capacity are both major determinants of the efficacy of LA.[11] Our understanding of the effects of circulating lipids on the efficacy of LA is limited.[12] To our knowledge, no study has thoroughly examined whether serum triglycerides (TG) alter the magnitude of the acute LA-induced reduction in LDL-C and Lp(a) in HoFH patients.

The objective of this study was to investigate how pre-LA serum TG concentrations influence the efficacy of LA in the treatment of HoFH. The association between pre-LA serum TG concentrations and the efficacy of LA using heparin-induced extracorporeal LDL precipitation (HELP) or dextran sulfate adsorption (DSA) to acutely reduce LDL-C and Lp(a) levels was examined in a sample of patients with HoFH. We hypothesized that pre-LA TG concentrations would be negatively associated with an acute, LA-induced reduction of LDL-C and Lp(a) in HoFH patients, independent of the type of LA system used.

Materials and Methods

Patients

Ten HoFH patients and five compound heterozygous patients with genetically defined *LDLR* mutations were included in this study. The HoFH patients were carriers of the W66G mutation in exon 3 (n=3),[13] the >15-kb deletion at the 5' end of the gene (n=5),[14] the splice site mutation in intron 7 (LDLR1061(-1) G to C) (n=1)[15] and the C660X Lebanese alleles (n=1).[16] Four compound heterozygous subjects were carriers of the W66G mutation and the >15-kb deletion and one subject was a carrier of the C646Y mutation in exon 14[17] and the >15-kb deletion. The >15-kb deletion at the 5' end of the gene, the splice site mutation in intron 7, the C646Y mutation in exon 14 and the C660X

mutation were considered receptor-negative mutations. The W66G point mutation in exon 3 was categorized as a receptor-defective mutation. All subjects were treated with maximally tolerated doses of statin and ezetimibe during the duration of the study.

Study design

Data from consecutive LA treatments (n=2124) performed between August 2008 and February 2016 at the CHU de Québec-Laval University were collected. For each patient, the compiled data included, when available: 1) the date of LA, 2) the cumulative number of LA treatments received, 3) the interval (in days) between LA treatments, 4) the type of LA system used, 5) the volume of plasma that was filtered per treatment, 6) the duration (in minutes) of the treatments, 7) the pre- and post-LA serum lipid concentrations and 8) the cumulative interval since the first LA treatment (in days). The LA-induced acute decrease in serum lipids was calculated as the percent difference between the post-LA and pre-LA serum lipid concentrations. This study was approved by the Laval University Medical Center ethical review committee and informed consent was obtained from each patient.

LA systems

The HELP and the DSA LA systems were used in this study. HELP LA was performed using the Plasmat Futura® system (B. Braun Medical, Bethlehem, PA, USA). The maximum volume of plasma that could be filtered using this system was 3000 mL, until late 2015 when new filters that increased the maximum volume of plasma that could be filtered to 4000 mL were made available in Canada. LA by DSA was performed using the Liposorber® LA-15 system (Kaneka Corporation, Osaka, Japan). This system has been used at the Lipid Clinic of the CHU de Québec-Laval University since 2012. The technical procedures for the HELP and DSA systems have been previously described.[11] All subjects experienced the two LA systems during the study period.

Determination of serum lipid concentrations

For routine LA therapy, patients are not instructed to fast before treatments. Blood samples were obtained pre- and post-LA. Serum cholesterol and TG concentrations were determined with a Roche/Hitachi MODULAR analyzer (Roche Diagnostics, Indianapolis, IN, USA) using the appropriate reagents. The LDL-C concentration was calculated using the Friedewald equation.[18] In 24 out of 2124 treatments (1.1% of the total compiled treatments), the LDL-C concentration was not calculated because the TG concentration was > 4.50 mmol/L. Lp(a) concentrations were measured by nephelometry using a BN ProSpec system (Siemens Healthcare, Erlangen, Germany).

Statistical analyses

Statistical analyses were conducted with the JMP Pro software v12.2.0 using mixed models for repeated measures. In the models, the acute LA-induced reduction in lipid concentrations was the dependent variable. Pre-LA TG concentrations and other potential covariates were included in the

models as independent variables and were treated as fixed effects. Subjects were treated as a random effect. The patient-specific time interval since the first compiled LA for each treatment was treated as the repeated measure in the models. The spatial power covariance structure was used for all the models because the time intervals between treatments were unequally spaced. The models only included treatments without missing covariates and with TG concentrations < 4.50 mmol/L, i.e. models with the acute LA-induced reduction in LDL-C as a dependent variable included n=1761 treatments and models with the LA-induced acute decrease in Lp(a) as a dependent variable included n=1391 treatments. The normality of the models was assessed using the distribution of the scaled residual values. The Tukey-Kramer adjustment was used for multiple comparison tests. Statistical significance was set to p <.05.

Results

The mean age of the patients in this study was 34.2 ± 14.3 years (**Table 1**). They were treated with maximally-tolerated doses of statins (atorvastatin: 80 mg, n=7; 40 mg, n=1; rosuvastatin: 40 mg, n=6; 5 mg, n=1) and ezetimibe (10 mg; n=14). Eight subjects had a history of CAD at baseline. Patients exhibited typical characteristics of HoFH, elevated concentrations of total-C, LDL-C and Lp(a). Prior to the first compiled LA, patients with receptor-negative HoFH exhibited higher total-C and LDL-C concentrations than patients with receptor-defective HoFH. Although carriers of the receptor-negative mutations exhibited approximately 2-fold higher average TG concentrations than carriers of the double receptor-defective mutations, the difference was not significant (p=.2). There was no difference in the Lp(a) concentrations between the *LDLR* genotypic groups (p=.5). There was considerable intra-genotype variability in Lp(a) concentrations (defective/defective, range: 374-692 mg/L; defective/negative, range: 419-1,140 mg/L; negative/negative, range: 121-1,500 mg/L).

As presented in **Table 2**, the use of the two systems between the *LDLR* genotypes was unequal (p <.0001). Patients with double receptor-negative mutations were treated more often with the DSA system than patients with receptor-defective mutations. The average volume of filtered plasma per treatment was significantly higher in patients with double receptor-negative mutations, likely due to the more frequent use of the DSA system.

A significant association between pre-LA TG concentrations and the acute LA-induced reduction in LDL-C, modified by the type of LA system, was observed ($p_{\text{pre-LA TG quartile * LA system}}$=.04). The acute reduction in LDL-C using the DSA system was 3.9% lower when pre-LA TG concentrations were >2.09 mmol/L (highest quartile) than when pre-LA TG concentrations were ≤0.93 mmol/L (lowest quartile) (-59.4 ± 3.1% vs. -63.3 ± 3.0%, p=.007) (**Figure 1**). However, pre-LA TG concentrations had no effect on the reduction in LDL-C when the HELP system was used ($p_{\text{inter-quartiles}}$ ≥.7). The interaction between the type of LA system used and the pre-LA TG concentrations on the LA-induced acute reduction in LDL-C was independent of the *LDLR* genotype, type of lipid-lowering medication,

cumulative number of LA treatments, volume of plasma that was filtered, LA treatment frequency, cumulative interval since the first compiled LA and the pre-LA LDL-C concentrations. Similar results were obtained when the analysis was conducted on the absolute reduction in concentrations of LDL-C (mmol/L).

Significant associations between pre-LA TG concentrations and the acute LA-induced reduction in non-HDL-C and in total-C, modified by the type of LA system, were observed (non-HDL-C: $p_{\text{pre-LA TG quartile * LA system}}$=.03; total-C: $p_{\text{pre-LA TG quartile * LA system}}$=.04). The acute reduction in non-HDL-C and total-C using the DSA system was reduced by respectively 3.8% (p=.008) and 3.7% (p=.004) when pre-LA TG concentrations were >2.09 mmol/L (highest quartile) compared with pre-LA TG concentrations ≤0.93 mmol/L (lowest quartile) (**Figure 2A** and **B**). Pre-LA TG concentrations were not associated with the LA-induced acute reduction in non-HDL-C and total-C when the HELP system was used ($p_{\text{inter-quartiles}} \geq .9$).

The LA-induced acute reduction in HDL-C was significantly more important using the HELP system (p <.0001), independent of pre-LA TG levels. The acute reduction in HDL-C was lower when pre-LA TG concentrations were >2.09 mmol/L (highest quartile) than when pre-LA TG concentrations were ≤0.93 mmol/L (lowest quartile) using both the DSA system (-7.1 ± 2.3% vs. -10.1 ± 2.4%, p=.002) and the HELP system (-18.5 ± 2.1% vs. -20.8 ± 2.1%, p=.002) (**Figure 2C**).

Pre-LA TG concentrations were inversely associated with the acute LA-induced reduction in TG. The acute reduction in TG was lower when pre-LA TG concentrations were >2.09 mmol/L (highest quartile) compared with pre-LA TG concentrations ≤0.93 mmol/L (lowest quartile) using both the DSA system (-55.6 ± 6.6% vs. -25.3 ± 6.8%, p <.0001) and the HELP system (-47.2 ± 6.0% vs. -38.4 ± 5.9%, p=.0009) (**Figure 2D**).

Supplemental Table 1 presents the comprehensive, non-adjusted, absolute, pre-LA, post-LA and LA-induced reduction in lipid concentrations.

No association was observed between the pre-LA TG concentrations and the LA-induced acute decrease in Lp(a) (p=.2). The systems also had no differential effect on the reduction of Lp(a) concentration ($p_{\text{pre-LA TG * LA system}}$=.7). The observations were similar when the analysis was conducted on the absolute reduction in Lp(a) concentration (mg/L).

Compared with LA by HELP, LA by DSA induced a relatively less important decrease in LDL-C (Δ=-4.7 ± 0.6%, p <.0001) and Lp(a) (Δ=-4.6 ± 1.0%, p <.0001) levels over the duration of the study after adjusting for pre-LA TG levels and the volume of plasma that was filtered. However, without the adjustment for the filtered plasma volume, LA by DSA was more effective than LA by HELP in reducing serum concentrations of LDL-C (Δ=+8.9 ± 0.6%, p <.0001) and Lp(a) (Δ=+5.1 ± 0.9%, p

<.0001). The average volume of filtered plasma per treatment was significantly higher with DSA than with HELP (4,147 ± 706 vs. 2,961 ± 204 mL, *p* <.0001).

Discussion

This retrospective longitudinal study evaluated how pre-LA TG concentrations modified the efficacy of two different LA systems to acutely reduce the concentrations of LDL-C and Lp(a) in patients with HoFH. Our observations demonstrate that elevated pre-LA serum TG concentrations attenuated the acute decrease in LDL-C when using the DSA system, but not when using the HELP system. These observations were independent of various factors associated with LA efficacy, namely, pre-LA LDL-C or Lp(a) concentrations, the volume of filtered plasma, the *LDLR* genotype, and the interval between consecutive treatments. Our data suggest that LA therapy should be adapted according to pre-LA TG concentrations to maximize its efficacy among patients with HoFH.

In the DSA system, after primary separation, the plasma is pumped into one of two DSA columns. ApoB-containing lipoproteins electrostatically bind to the negatively charged dextran sulfate cellulose beads. The plasma is then transferred to the other column and the first column is rinsed to remove the apoB-containing lipoproteins. Both columns work in rotation during treatment. It is estimated that 2.5 grams of lipoproteins can be adsorbed by each column every cycle.[19] The plasma is then mixed with blood, passes through a warmer column, and is re-injected into the patient's venous circulation. Heparin is used as an anticoagulant during the treatment.[10] In the HELP system, after primary separation from the other constituents of the blood, the plasma is mixed with heparin and an acetate-acetic acid buffer to reduce the pH of the mixture to approximately 5. At this pH, apoB-containing particles are negatively charged and heparin is positively charged.[10] After the plasma has been mixed thoroughly with the acetate-acetic acid buffer and heparin, LDL-heparin complexes are formed and precipitate in the acidic environment. These precipitates are removed from the plasma by polycarbonate membrane filtration. Finally, the remaining free heparin is removed by adsorption, the acidic plasma is returned to a physiological pH value, and the LDL-depleted plasma is returned to the patient's venous circulation.[10]

Based on our observations, the interaction between apoB-containing lipoproteins and dextran sulfate is reduced when the total serum TG concentrations are high, when the TG-content of apoB-containing particles is elevated or when the LDL particles are small and dense.[20] The electrostatic affinity between apoB-particles and dextran sulfate is likely impaired in TG-rich plasma. It is also possible that the adsorption of large TG-rich apoB-containing particles reduces the residual available contact surface between the apoB particles and dextran-sulfate. Finally, small cholesterol-rich LDL particles, highly prevalent in the plasma of HoFH patients with high TG levels,[20] may have a reduced affinity for dextran sulfate compared with larger particles. Moreover, since pre-LA TG concentrations were not associated with an acute LA-induced reduction in Lp(a) levels, the presence of apo(a) on LDL

particles compared with LDL alone may enhance the interaction between the adsorbate and the adsorbent. The efficacy of the HELP system to acutely reduce LDL-C and Lp(a) levels was not impaired by pre-LA TG concentrations. Based on the technical procedures of this system, we hypothesized that, independent of plasma TG concentrations, lipoprotein TG-content or LDL size, the mixing step prior to precipitation allows for a large contact surface area between apoB-containing particles and heparin. Extensive studies are required to characterize the exact mechanism underlying the observed effects.

We observed that the LA-induced acute reduction in HDL-C levels was more important with the HELP system than with the DSA system. Elevated plasma levels of apoE-rich HDL particles is a phenotypic characteristic of FH.[21] Moriarty et al[22] previously observed that LDL apheresis using HELP and DSA acutely reduces the plasma levels of apoE. The reduction in apoE was associated with the pre vs. post change in HDL-C. Although HDL is a negatively charged particle, apoE is positively charged and interacts with heparin and dextran sulfate.[22] ApoE is suspected to be responsible of the LA-induced acute reduction in HDL-C. Investigation is required to identify mechanisms underlying the differential effect of LA with HELP and DSA on HDL-C removal.

Despite the reduced efficacy associated with elevated TG levels, LA by DSA remained more effective than LA by HELP for the acute removal of LDL-C from plasma because of its higher filtration capacity (>4000 mL vs. ≤4000 mL), independent of TG concentrations, as previously observed.[11] In an era of precision medicine, these observations may be translated into practical proceedings to maximize the efficacy of LA by DSA. When conducting LA by DSA in HoFH patients, a filtration volume >4,000 mL should be targeted. Otherwise, LA by HELP remains more effective. Additionally, these data underscore the importance of lifestyle interventions (weight management and dietary counseling) in HoFH patients with hypertriglyceridemia.

In this study, the number of LA treatments using DSA in patients with double receptor-defective mutations was very limited. Although the analyses were adjusted for the *LDLR* genotype, it remains unclear whether the efficacy of LA with DSA was inversely associated with TG levels in subjects with double receptor-defective mutations. Hypertriglyceridemia is not a typical phenotypic characteristic of HoFH but it is well recognized that VLDL apoB-100 secretion is inversely associated with LDLR functionality.[23, 24] The average fasting TG levels in patients with receptor-negative mutations were higher than those with receptor-defective mutations. The inverse association between pre-treatment TG concentrations and the efficacy of LA by DSA is particularly relevant for patients with double receptor-negative mutations. Therefore, the data from this study underscores the fact that these patients should be treated more intensively than patients with receptor-defective HoFH, as previously suggested.[25]

The major strengths of this study are the number of consecutive treatments on which the study is based, the duration of the patient follow-ups, and the statistical approaches used. Conversely, the study results come from a limited number of patients, most of whom were carriers of mutations that are highly prevalent in the French-Canadian population. A similar assessment among patients carrying other common *LDLR* mutations is warranted. The main limitation of the study is the use of the Friedewald equation for the determination of the LDL-C in non-fasting samples. This equation is based on the assumption that the mass ratio of plasma TG to VLDL-C is constant.[18] The calculation of the LDL-C in non-fasting samples may lead to underestimation of LDL-C.[26] In the present study, although samples were not obtained at fast, data from treatments with TG levels above the cut-point of the Friedewald equation (4.50 mmol/L) were excluded from the analyses. Evidence also suggests that the Friedewald equation is less accurate when LDL-C is very low, that can be the case post-LA.[27] In this context, caution should be exercised when evaluating the efficacy of LA in HoFH using LDL-C concentrations. Nonetheless, the inverse association between pre-LA TG concentrations and non-HDL-C observed with the DSA system supports the notion that pre-LA TG levels reduce the efficacy of this system, independent of the imprecision of the Friedewald equation. The non-randomized design and the unequal use of the two LA systems are also limitations.

In conclusion, this study demonstrated that the efficacy of LA using DSA, but not HELP, is inversely associated with pre-LA TG concentrations in patients with HoFH. Considering the life-long, repetitive aspect of LA therapy in HoFH, this inverse association is clinically relevant. Additionally, this study emphasizes the importance of adapting LA therapy to the severity of the disease to optimize its efficacy. Assessment of the association between pre-LA TG concentrations and the LA-induced acute reduction in apo A-1 and LDL apo B would be required in further studies to corroborate the present conclusions.

Conflicts of interest

PC has received funding in the last 5 years from the Canadian Institutes of Health Research, Agriculture and Agri-Food Canada, Merck, Pfizer, Atrium Innovations and the Kaneka Corporation. BL has received funding in the last 5 years from the Canadian Institutes of Health Research, the Natural Sciences and Engineering Research Council of Canada, Agriculture and Agri-Food Canada, Pfizer, Atrium Innovations and Merck. JPDC is the recipient of doctoral scholarships from the Canadian Institutes of Health Research and the Fonds de Recherche du Québec – Santé. The other authors report no conflicts of interest.

Author contributions

All the authors read and approved the final manuscript. PC designed the study and experiments; JPDC collected the data; JPDC, PC, and BL analyzed the data; JPDC, AJT, JB, BL, and PC wrote the manuscript; PC had primary responsibility for the final content.

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Tables

Table 9-1 Baseline demographic, genotypic and biochemical characteristics of HoFH patients based on their *LDLR* genotype[a]

	Defective/defective	Defective/negative	Negative/negative	*p*
Sex				.4
Women (n)	2	3	3	
Men (n)	1	1	5	
Age (y)	39.1 ± 20.8	37.1 ± 17.5	30.8 ± 11.2	.7
CAD history (n)	2	1	5	.4
LDLR mutations (n)				
W66G	3	-	-	
Del>15-KB	-	-	5	
$LDLR_{1061\ G\rightarrow C}$	-	-	1	
C660X	-	-	1	
C646Y+Del>15-KB	-	-	1	
W66G+Del>15-KB	-	4	-	
Total-C (mmol/L)	5.86 ± 0.58	12.70 ± 3.72*	13.49 ± 3.06*	.008
TG (mmol/L)	0.79 ± 0.11	1.68 ± 0.65	1.52 ± 0.73	.2
HDL-C (mmol/L)	1.41 ± 0.26	1.19 ± 0.52	0.95 ± 0.36	.2
LDL-C (mmol/L)	4.09 ± 0.44	10.74 ± 3.91*	11.85 ± 2.70*	.006
Non-HDL-C (mmol/L)	4.45 ± 0.39	11.51 ± 4.00*	12.55 ± 2.79*	.005
Total-C/HDL-C	4.22 ± 0.53	13.01 ± 9.11	15.27 ± 3.98*	.04
Lp(a) (mg/L)	497 ± 171	860 ± 332	616 ± 536	.5

[a] Data are presented as the mean ± standard deviation of the mean or frequency. Lipid values refer to serum concentrations before the first compiled lipoprotein apheresis treatment. LDLR: LDL receptor; CAD: coronary artery disease. *: multiple comparisons with Tukey adjustment vs defective/defective, $p<.05$.

Table 9-2 Technical aspects of lipoprotein apheresis treatments according to LDLR genotype[a]

	Defective/defective	Defective/negative	Negative/negative	*p*
LA treatments received before compilation (n)	33 ± 24	98 ± 73	125 ± 53	.09
consecutive compiled LA treatments (n)	137 ± 46	126 ± 21	149 ± 77	.8
interval between LA treatments (days)	17 ± 9	20 ± 9*	15 ± 14*†	<.0001
cumulative interval since the first compiled LA treatment (days)	2347 ± 435	2466 ± 7	2284 ± 557	.8
System				<.0001
HELP (n)	313	348	857	
DSA (n)	5	83	155	
Filtered plasma volume per treatment (mL)	2999 ± 130	3100 ± 457*	3176 ± 609*†	<.0001

[a] Data are presented as the mean ± standard deviation of the mean or the frequency. These data are based on the treatments included in the statistical models with the acute LA-induced reduction in LDL-C as a dependent variable (n=1761). HELP: heparin-induced extracorporeal LDL precipitation; DSA: dextran sulfate adsorption. *: multiple comparisons with Tukey adjustment vs defective/defective, p <.05; †: multiple comparisons with Tukey adjustment vs defective/negative, p <.05.

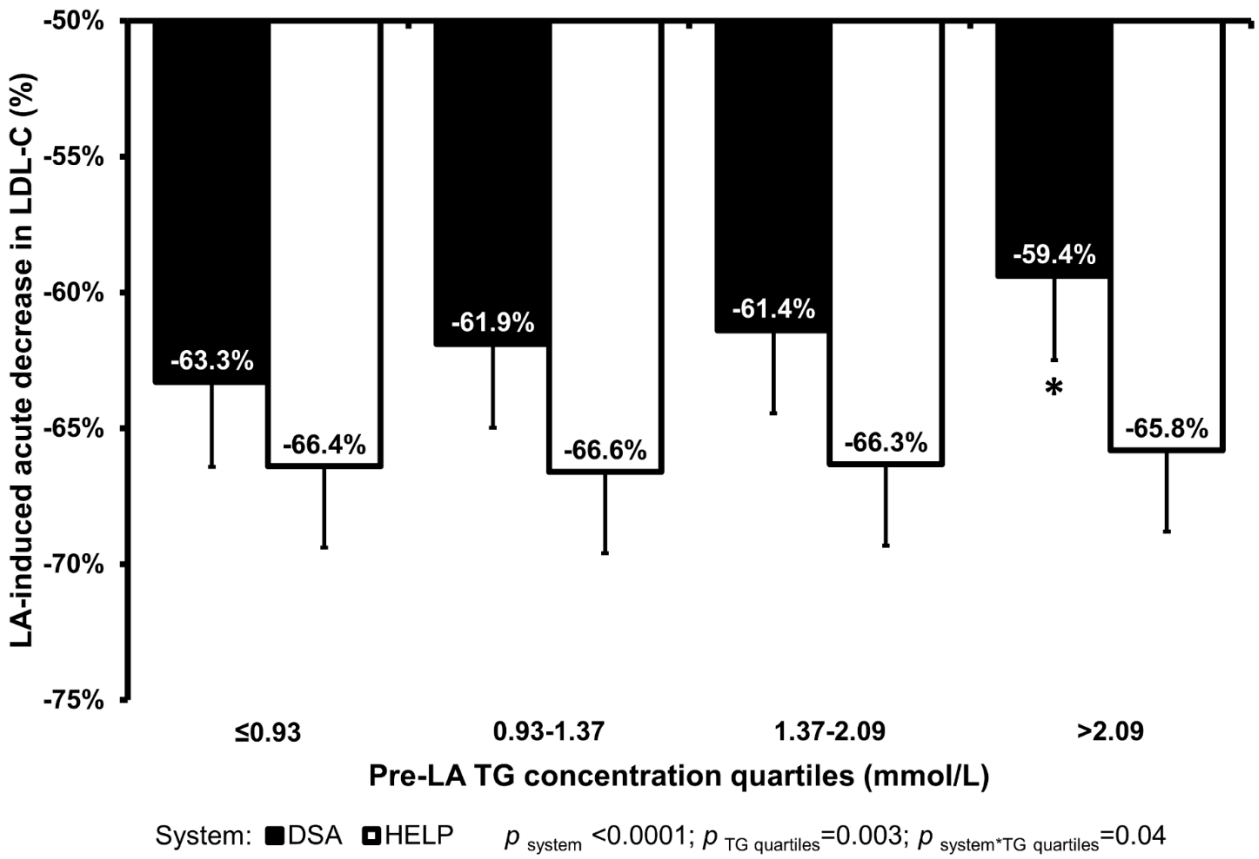
Table 9-3 Acute LA-induced reduction in LDL-C and Lp(a) concentrations according to the type of LA system and the volume of filtered plasma[a]

	HELP	**DSA**	**Δ**	***p***
Model 1				
LDL-C	-66.2 ± 3.0	-61.4 ± 3.1	-4.8 ± 0.6	<.0001
Lp(a)	-68.6 ± 5.1	-63.9 ± 5.2	-4.7 ± 0.9	<.0001
Model 2				
LDL-C	-62.7 ± 2.7	-71.5 ± 2.7	+8.8 ± 0.6	<.0001
Lp(a)	-65.3 ± 5.3	-70.4 ± 5.4	+5.1 ± 0.8	<.0001

[a] Data are presented as the mean percent of acute LA-induced reduction (± the standard error of the mean) and were calculated using a mixed model that included pre-LA TG and LDL-C/Lp(a) concentrations, the type of LA system used, the *LDLR* genotype, the interval between LA treatments, the interval since the first LA treatment, the type of statin therapy, the cumulative number of LA treatments as independent fixed covariates and the study subjects as a random effect. **Model 1**: With further adjustment for the volume of filtered plasma. **Model 2**: Without further adjustment for the volume of filtered plasma. The average volume of filtered plasma per treatment was significantly higher with DSA than HELP (4147 ± 706 vs. 2961 ± 204 mL; *p* <.0001). LA: lipoprotein apheresis; DSA: Dextran sulfate adsorption; HELP: Heparin induced extracorporeal LDL precipitation.

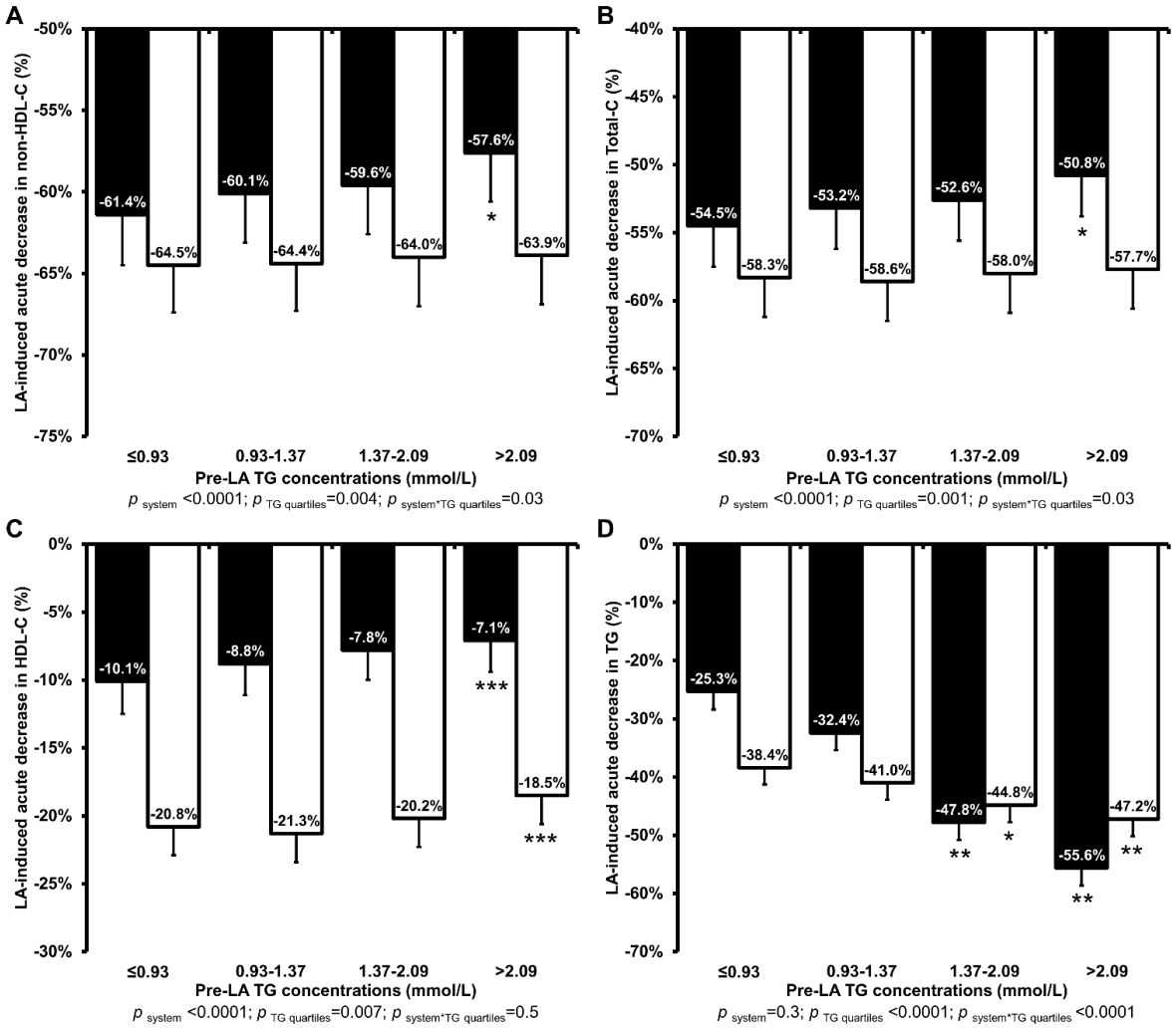
Figures

Figure 9-1 Mean acute, LA-induced decrease in LDL-C concentrations based on pre-LA TG concentrations and the LA system.



The mean acute, LA-induced decrease in LDL-C concentrations (%) based on pre-LA TG concentrations and the LA system in patients with homozygous familial hypercholesterolemia. Data are presented as the mean ± standard error of the mean. C: cholesterol; DSA: dextran sulfate adsorption; HELP: heparin-induced extracorporeal LDL precipitation; LA: lipoprotein apheresis; TG: triglycerides. *: p <.05 vs system-specific pre-LA TG ≤.93 mmol/L (quartile 1).

Figure 9-2 Mean acute, LA-induced decrease in lipid concentrations based on pre-LA TG concentrations and the LA system.



The mean acute, LA-induced decrease in (A) non-HDL-C, (B) total-C, (C) HDL-C, (D) triglyceride (TG) concentrations (%) based on pre-LA TG concentrations and the LA system in patients with homozygous familial hypercholesterolemia. Data are presented as the mean ± standard error of the mean. C: cholesterol; DSA: dextran sulfate adsorption; HELP: heparin-induced extracorporeal LDL precipitation; LA: lipoprotein apheresis; TG: triglycerides. ■: DSA system; □: HELP system; *: p <.05 vs system-specific pre-LA TG ≤ 0.93 mmol/L (quartile 1); **: p <.05 vs system-specific pre-LA TG ≤1.37 mmol/L (quartiles 1 and 2); ***: p <.05 vs system-specific pre-LA TG ≤2.09 mmol/L (quartiles 1, 2 and 3).

Supplemental material

Supplemental table 9-1 Mean non-adjusted pre-LA, post-LA and absolute LA-induced decrease in lipid concentrations based on pre-LA TG concentrations and the LA system.

	DSA				HELP			
	TG≤0.93	**0.93<TG≤1.37**	**1.37<TG≤2.09**	**TG>2.09**	**TG≤0.93**	**0.93<TG≤1.37**	**1.37<TG≤2.09**	**TG>2.09**
LDL-C (mmol/L)								
Pre-LA	8.49 ± 2.40	9.01 ± 2.26	8.71 ± 2.10	9.64 ± 2.46	6.19 ± 3.11	8.58 ± 3.20	10.33 ± 3.48	10.65 ± 3.84
Post-LA	2.19 ± 0.75	2.57 ± 1.19	2.27 ± 1.11	2.83 ± 1.84	2.39 ± 1.32	3.20 ± 1.54	4.16 ± 2.20	4.33 ± 2.32
Δ (mmol/L)	-6.30	-6.44	-6.44	-6.81	-3.80	-5.38	-6.16	-6.32
Δ (%)	-74.2	-71.5	-73.9	-70.7	-61.4	-62.7	-59.7	-59.4
Non-HDL-C (mmol/L)								
Pre-LA	8.83 ± 2.42	9.55 ± 2.27	9.47 ± 2.08	10.88 ± 2.56	6.55 ± 3.12	9.12 ± 3.21	11.12 ± 3.49	12.01 ± 3.94
Post-LA	2.46 ± 0.78	2.90 ± 1.08	2.69 ± 1.16	3.46 ± 1.82	2.61 ± 1.33	3.47 ± 1.54	4.53 ± 2.26	4.91 ± 2.47
Δ (mmol/L)	-6.38	-6.65	-6.78	-7.41	-3.94	-5.65	-6.59	-7.11
Δ (%)	-72.2	-69.6	-71.6	-68.2	-60.2	-62.0	-59.2	-59.1
Total-C (mmol/L)								
Pre-LA	9.71 ± 2.25	10.44 ± 2.21	10.59 ± 2.08	11.89 ± 2.56	7.82 ± 2.90	10.26 ± 3.08	12.06 ± 3.58	12.81 ± 4.13
Post-LA	3.21 ± 0.72	3.69 ± 1.05	3.66 ± 1.13	4.35 ± 1.76	3.62 ± 1.16	4.36 ± 1.44	5.28 ± 2.35	5.56 ± 2.64
Δ (mmol/L)	-6.49	-6.75	-6.93	-7.54	-4.21	-5.90	-6.78	-7.25
Δ (%)	-66.9	-64.6	-65.5	-63.4	-53.8	-57.5	-56.2	-56.6
HDL-C (mmol/L)								
Pre-LA	0.87 ± 0.29	0.89 ± 0.25	1.12 ± 0.49	1.01 ± 0.36	1.27 ± 0.36	1.15 ± 0.39	0.94 ± 0.37	0.80 ± 0.31
Post-LA	0.76 ± 0.26	0.79 ± 0.23	0.97 ± 0.39	0.89 ± 0.30	1.01 ± 0.30	0.89 ± 0.29	0.75 ± 0.28	0.65 ± 0.25
Δ (mmol/L)	-0.11	-0.10	-0.15	-0.12	-0.26	-0.26	-0.19	-0.15
Δ (%)	-12.9	-10.8	-13.7	-12.2	-20.7	-22.7	-20.7	-18.2
Lp(a) (mg/L)								
Pre-LA	802 ± 334	714 ± 468	776 ± 395	641 ± 384	605 ± 311	823 ± 362	775 ± 506	557 ± 562
Post-LA	208 ± 71	207 ± 120	210 ± 91	217± 250	216 ± 115	280 ± 146	307 ± 261	250 ± 306
Δ (mg/L)	-594	-507	-566	-424	-389	-543	-468	-307
Δ (%)	-74.1	-71.1	-72.9	-66.1	-64.3	-66.0	-60.4	-55.1
TG (mmol/L)								
Pre-LA	0.79 ± 0.09	1.17 ± 0.13	1.68 ± 0.21	2.71 ± 0.56	0.77 ± 0.11	1.15 ± 0.12	1.72 ± 0.21	2.78 ± 0.64
Post-LA	0.58 ± 0.31	0.77 ± 0.49	0.94 ± 0.50	1.39 ± 0.57	0.47 ± 0.14	0.59 ± 0.18	0.81 ± 0.29	1.22 ± 0.59
Δ (mmol/L)	-0.21	-0.40	-0.75	-1.32	-0.30	-0.56	-0.91	-1.56
Δ (%)	-26.1	-34.2	-44.4	-48.8	-39.3	-48.6	-53.0	-56.1

[a] Data are presented as the mean ± standard deviation of the mean.