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Anne C Goldberg
Washington University School of Medicine in St. Louis

Richard L Dunbar
University of Pennsylvania

Linda Hemphill
Harvard University

Stephan P Babirak
Metabolic Leader, LLC

Gerald Wilson
Regeneron Pharmaceuticals, Inc.

See next page for additional authors

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Original Article

A retrospective analysis of clinical use of alirocumab in lipoprotein apheresis patients

Anne C. Goldberg, MD*, Richard L. Dunbar, MD, Linda Hemphill, MD, Stephan P. Babirak, MD, PhD, Gerald Wilson, PharmD, Michael Wooten, PharmD, Mohamed Iydroose, PharmD, Kelley Dacus, PharmD, Heather Minchew, MD, Julie-Ann Dutton, MD, Patrick M. Moriarty, MD

Division of Endocrinology, Metabolism and Lipid Research, Department of Medicine, Washington University School of Medicine, St. Louis, MO, USA (Dr. Goldberg); Perelman Center for Advanced Medicine, University of Pennsylvania, Philadelphia, PA, USA (Dr. Dunbar); Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA (Dr. Hemphill); Metabolic Leader, LLC, Scarborough, ME, USA (Dr. Babirak); Regeneron Pharmaceuticals, Inc., Tarrytown, NY, USA (Drs. Wilson, Iydroose and Dacus); and Department of Internal Medicine, Division of Clinical Pharmacology, University of Kansas Medical Center, Kansas City, KS, USA (Drs. Minchew, Dutton and Moriarty)

KEYWORDS:
Apheresis;
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BACKGROUND: The previously published ODYSSEY ESCAPE trial demonstrated a significant reduction in the use of lipoprotein apheresis for heterozygous familial hypercholesterolemia (HeFH) patients when placed on alirocumab 150 mg every 2 weeks. In patients with HeFH who have consistently elevated levels of low-density lipoprotein cholesterol (LDL-C) despite maximally tolerated statin therapy, current lipid guidelines recommend apheresis. Although apheresis reduces LDL-C levels by 50%–75%, it must be repeated, as frequently as every 1–2 weeks.

OBJECTIVE: To assess clinical experience with apheresis and alirocumab for patients in a real-world practice setting.

METHODS: This retrospective review included patients from 5 apheresis centers who were treated with apheresis and had started alirocumab therapy. In addition to LDL-C levels, total cholesterol, high-density lipoprotein cholesterol (HDL-C), non-HDL-C, triglycerides, and particle numbers were evaluated if data were available.

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* Corresponding author. Washington University School of Medicine, 660 S Euclid Ave, Campus Box 8127, St. Louis, MO 63110, USA.
E-mail address: agoldber@wustl.edu

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RESULTS: Eleven of the 25 (44%) patients discontinued apheresis completely after initiation of alirocumab therapy, having achieved LDL-C <70 mg/dL or >50% reduction from baseline levels. Among the 14 patients who remained on apheresis, seven decreased the frequency of apheresis sessions. No significant safety problems were reported.

CONCLUSION: Alirocumab lowered LDL-C levels by an average of 55.5% in patients receiving apheresis for elevated LDL-C. Seventy-two percent of patients on alirocumab therapy discontinued or reduced the frequency of apheresis treatment. However, some patients continued to require apheresis due to elevated lipoprotein(a), extremely elevated LDL-C, or if alirocumab therapy was discontinued due to less than anticipated LDL-C reduction.

Introduction

Familial hypercholesterolemia (FH) is a common, treatable, genetic metabolic disorder. FH is due to mutations in the low-density lipoprotein (LDL) receptor gene, as well as defects in genes encoding apolipoprotein B and proprotein convertase subtilisin/kexin type 9 (PCSK9).

Patients with heterozygous FH (HeFH) often have LDL-cholesterol (LDL-C) ≥100 mg/dL, despite maximally tolerated statin and other lipid-lowering therapies.[1,2] Lipoprotein apheresis directly removes lipoproteins containing apolipoprotein B and is indicated by the US Food and Drug Administration (FDA) to treat inadequately controlled hypercholesterolemia.[3,4] The procedure can acutely reduce LDL-C by 50%–75%; however, levels return to baseline within days to a few weeks, and repeated apheresis is required to maintain this reduction.[4,5] Apheresis is time-consuming, usually conducted weekly or every 2 weeks (Q2W), costly, and can only be performed in apheresis centers, with locations that may not be readily accessible in some regions.[3,5]

Lipid guidelines at the time of this retrospective review recommended apheresis for patients with HeFH and a baseline LDL-C of ≥190 mg/dL with inadequate response to maximally tolerated statin therapy, or those with statin intolerance with persistently elevated LDL-C levels with or without ezetimibe and PCSK9 inhibitor therapies.[3,6] Recently, apheresis was granted FDA approval at a lower LDL-C threshold of ≥100 mg/dL in patients with HeFH and documented coronary artery or peripheral arterial disease.[7]

The monoclonal antibody to PCSK9, alirocumab, has demonstrated lowering of LDL-C levels by up to 61% in patients with and without HeFH with a dosing regimen of 150 mg Q2W.[8] The previously published ODYSSEY ESCAPE trial (NCT02326220) was a double-blind study designed to evaluate the effect of alirocumab vs placebo on the frequency of apheresis in patients with HeFH (n = 62), with the primary efficacy endpoint being the rate of apheresis treatments over a 12-week treatment period. The previously published results of ODYSSEY ESCAPE showed that alirocumab 150 mg Q2W significantly decreased the frequency (75% additional reduction in the rate of apheresis vs placebo; $P < .0001$) or the necessity for apheresis in a clinical setting.[9]

This retrospective analysis evaluated the real-world effect of adding alirocumab treatment in patients undergoing apheresis.

Methods

This was a multicenter retrospective analysis using de-identified data collected by retrospective chart review pooling 25 patients from 5 apheresis centers in the US. The analysis included patients who were at least 18 years of age, had been on apheresis for at least 2 months prior to alirocumab treatment, and started alirocumab therapy at any time after July 25, 2015 (ie, after FDA approval of alirocumab). Although two of the centers participated in ODYSSEY ESCAPE, patient data from the ESCAPE study[9] were excluded from this analysis, to avoid duplication. Diagnosis of HeFH was made either by genotyping or by clinical criteria that were based on either World Health Organization/Dutch Lipid Clinical Network criteria[10] with a score of >8 points, or Simon Broome criteria with a criterion for definite FH.[11] The collected data included demographic data, diagnosis, medications, history of cardiovascular events, LDL-C levels before and after apheresis sessions, frequency of apheresis, and LDL-C levels after initiation of alirocumab therapy. Additional lipid parameters (total cholesterol, high-density lipoprotein cholesterol [HDL-C], non-HDL-C, and triglycerides) were included if available. Safety events related to alirocumab treatment and apheresis were requested as part of data collection.

All patients received alirocumab 75 mg or 150 mg Q2W administered subcutaneously, depending on their physician's judgment. Patients were categorized according to their apheresis status after alirocumab treatment: discontinued apheresis, decreased apheresis frequency, or unchanged apheresis frequency. Individuals were used as their own controls for different calculations. Baseline, lipid, and safety data were summarized by descriptive statistics only, and no formal statistical analysis was planned.

Results

All patients had HeFH, and 96% of patients had coronary artery disease, while 88% of patients were in

secondary prevention. The frequency of apheresis was Q2W in 24 patients (96%) and every 3 weeks for 1 patient (4%). Seven patients (28%) were taking a statin with or without additional lipid-lowering therapy. Eighteen patients (72%) were not on a statin due to statin intolerance (Table 1).

Initially, 7 patients received alirocumab 75 mg Q2W and 18 received 150 mg Q2W. In the alirocumab 75 mg Q2W group, 1 patient received dose adjustment to 150 mg Q2W. Patients had received alirocumab therapy for 8–52 weeks at the time of data collection.

Individual LDL-C data for each patient by apheresis status following alirocumab therapy are presented in Figure 1. Following alirocumab treatment, LDL-C levels were reduced by 55.5%, resulting in 44% of patients (n = 11) discontinuing apheresis, 28% (n = 7) decreasing the frequency of apheresis from Q2W to every 4 weeks, and 28% (n = 7) continuing the same apheresis frequency (Table 2; Fig. 1). Of the 11 patients who discontinued apheresis, 9 were able to achieve LDL-C reductions greater than 50% with alirocumab alone, and 5 had LDL-C < 70 mg/dL. Following apheresis, LDL-C levels were reduced by 60.7% (Table 2).

In patients discontinuing apheresis, LDL-C levels were reduced by 61.3% post-apheresis treatment and 62.2% post-alirocumab therapy (Table 3). In patients reducing apheresis frequency and those remaining on the same apheresis frequency, the LDL-C reductions were greater post-apheresis treatment (68.0% and 53.7%, respectively) compared with post-alirocumab LDL-C reductions (49.4% and 45.0%, respectively; Table 3).

For patients receiving alirocumab 75 mg Q2W and for those receiving alirocumab 150 mg Q2W, pre-apheresis and pre-alirocumab LDL-C levels were similar (Table 4). For the alirocumab 150 mg Q2W group, post-apheresis LDL-C reduction was 57.3%, and post-alirocumab LDL-C reduction was 56.6%. For patients receiving alirocumab 75 mg Q2W, the LDL-C reductions were 68.2% (post-apheresis) and 52.7% (post-alirocumab).

The mean post-alirocumab percent changes from baseline in other lipids for patients with data were –36.0% (total cholesterol), –44.1% (non-HDL-C), –46.4% (LDL particle number), –10.7% (triglycerides), and +2.7% (HDL-C; Fig. 2). Some patients had LDL-C levels that were the same with either alirocumab or apheresis. For some of these patients, shared decision-making between the patient and clinician led to the decision to discontinue apheresis based on issues of travel and time needed for apheresis. There were other patients who continued with apheresis due to very high lipoprotein (a) levels.

In total, 28% (n = 7) of patients treated with apheresis reported adverse events. Vascular access problems were reported in 16% of patients, as well as hypotension (4%), flushing (4%), and anemia (4%). Following alirocumab treatment, no adverse events were reported.

Discussion

This retrospective study assessed real-world experience with alirocumab in patients with HeFH being treated at apheresis clinics. Periodically administered apheresis has been an effective means of lowering serum lipids in patients with high cardiovascular risk.[12] Apheresis can be complementary to lipid-lowering therapy in patients with extremely elevated LDL-C levels.[6,12]

Table 1 Patient characteristics

Characteristic	Alirocumab (n = 25)
Age, y, mean (SD)	64.6 (8.45)
Gender, male, n (%)	8 (32)
Race, white, n (%)	24 (96)
Weight, kg, mean (SD)	81.3 (17.9)
HeFH diagnosis, n (%)	
WHO/Simon Broome Criteria	23 (92)
Genotyping	2 (8)
Coronary artery disease, n (%)	24 (96)
Secondary prevention	22 (88)
Arteriovenous fistula, n (%)	12 (48)
Statin intolerance, n (%)	18 (72)
Taking a statin	7 (28)
Other LLTs	Omega 3 fatty acids, niacin, fenofibrate, ezetimibe
Duration of apheresis, mean (range)	64.3 mo (7 months–14 years)
Apheresis frequency, n (%)	
Q2W	24 (96)
Q3W	1 (4)

HeFH, heterozygous familial hypercholesterolemia; LLT, lipid-lowering therapy; Q2W, every 2 wk; Q3W, every 3 wk; SD, standard deviation; WHO, World Health Organization. Statin intolerance, not taking any statin at any dose.

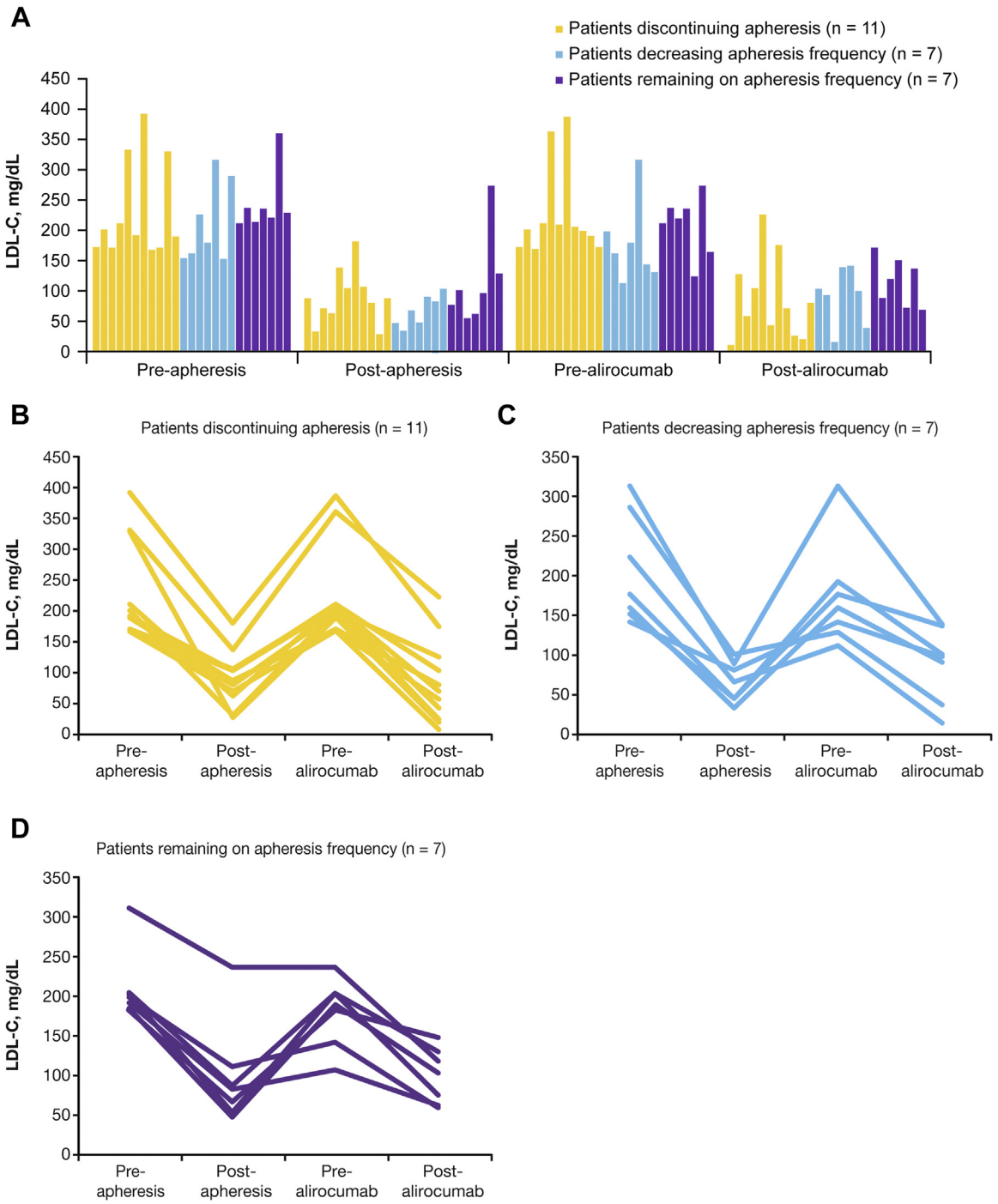

Figure 1 LDL-C levels of individual patients according to apheresis treatment and alirocumab treatment: (A) combined LDL-C levels, (B) patients discontinuing apheresis, (C) patients decreasing apheresis frequency, and (D) patients with unchanged apheresis frequency. LDL-C, low-density lipoprotein cholesterol.

Apheresis is expensive, with one apheresis session costing $1617–8000 depending on the country ($42,000–114,000 yearly for biweekly treatment).[13] In the USA, the initial cost of a year's supply of alirocumab was $14,600, although it has been reduced to $5850. Additional considerations for patients initiating apheresis therapy include the burden of frequently returning to apheresis centers for 2–3-hour apheresis procedures, as well as the frequent need for an arteriovenous fistula or other vascular access. After careful discussion between the patients and their clinicians, some patients had apheresis therapy discontinued despite LDL-C levels remaining above treatment thresholds. Factors contributing to the decision to discontinue apheresis in these patients included the time burden associated with frequent apheresis procedures, as well as patient's quality of life.

Table 2 Summary of pre- and post-treatment LDL-C levels for apheresis and alirocumab 75/150 mg Q2W treatment

LDL-C values	Apheresis (n = 25)	Alirocumab 75/150 mg Q2W (n = 25)
Pre-treatment LDL-C, mg/dL [mmol/L], mean (Min:Max)	226.6 (143.1:390.6) [5.86 (3.70:10.10)]	206.5 (113.3:386.7) [5.34 (2.93:10.00)]
Post-treatment LDL-C, mg/dL [mmol/L], mean (Min:Max)	89.3 (28.2:272.6) [2.31 (0.73:7.05)]	94.4 (8.1:222.4) [2.44 (0.21:5.75)]
LDL-C change, %, mean (Min:Max)	−60.7 (24.1:91.5))	−55.5 (19.1:95.3)

Pre- and post-apheresis LDL-C values were taken immediately before and after apheresis; for 3 patients, the post-apheresis LDL-C sample was taken at a later apheresis treatment date to the pre-apheresis LDL-C sample. The pre- and post-alirocumab LDL-C values are summarized for all patients, irrespective of apheresis status at the time of alirocumab treatment.

Alirocumab 75/150 mg Q2W, alirocumab 75 mg Q2W or 150 mg Q2W (depending on physician's judgment); LDL-C, low-density lipoprotein cholesterol; Q2W, every 2 wk; Max, maximum; Min, minimum.

Worldwide, only about 2500 patients are treated regularly with apheresis.[14] PCSK9 inhibitors may provide an alternative to apheresis for effectively reducing LDL-C levels in patients with elevated LDL-C despite statin therapy or those who are unable to tolerate statins. A significant number of patients in this study continued apheresis. There may be an added benefit from apheresis in patients who require aggressive lipid-lowering and are not at goal despite multiple drug therapy. Patients with elevated lipoprotein (a) levels also benefit from apheresis, and some continued the treatment for that reason. Alirocumab has helped people who require apheresis and who have not achieved their lipid goals despite apheresis. Some patients who are at the highest risk can benefit from multiple drug therapy, including PCSK9 inhibition, in addition to apheresis.

In this study, there were no adverse events reported with alirocumab, and the LDL-C reduction was consistent with clinical trial results from patients with and without HeFH in the alirocumab ODYSSEY program.[15,16] The lipid reduction and effect on apheresis frequency were similar to those of ODYSSEY ESCAPE, suggesting that the clinical trial experience translated to the clinical practice setting.[9] A large percentage of patients in this retrospective study reported complete statin intolerance (ie, were receiving no statin). The remainder (28%) were receiving a statin.

Patients with statin intolerance and moderately elevated LDL-C levels were previously treated with non-statin lipid-lowering therapies (excluding PCSK9 inhibitors) such as ezetimibe, which has been demonstrated to reduce LDL-C levels by 18% as monotherapy and 25% as statin add-on therapy.[17,18] Previously, for patients with HeFH, statin intolerance, and elevated levels of LDL-C, apheresis was the only effective means of reducing their LDL-C levels and lowering their cardiovascular risk.[6,17]

Treatment with alirocumab 75 mg or 150 mg Q2W enables some patients with HeFH to terminate or reduce the frequency of apheresis, which has a potential effect on costs and time spent with medical procedures.[13] In addition, alirocumab treatment provides a steady LDL-C reduction, while apheresis is associated with a "seesaw effect"; a

Table 3 LDL-C levels before and after apheresis or alirocumab treatment according to apheresis treatment

Mean (SD), mg/dL [mmol/L (SD)]	Patients discontinuing apheresis (n = 11)	Patients reducing apheresis frequency (n = 7)	Patients remaining on the same apheresis frequency (n = 7)
LDL-C following apheresis			
Pre-apheresis	228.5 (80.4) [5.91 (2.08)]	208.8 (68.8) [5.40 (1.78)]	242.5 (51.8) [6.27 (1.34)]
Post-apheresis	88.6 (43.7) [2.29 (1.13)]	66.9 (25.5) [1.73 (0.66)]	112.1 (74.6) [2.90 (1.93)]
Change, %	−61.3	−68.0	−53.7
LDL-C following alirocumab			
Pre-alirocumab	223.9 (75.4) [5.79 (1.95)]	176.3 (67.3) [4.56 (1.74)]	208.0 (49.9) [5.38 (1.29)]
Post-alirocumab	84.7 (67.3) [2.19 (1.74)]	89.3 (47.2) [2.31 (1.22)]	114.5 (39.8) [2.96 (1.03)]
Change, %	−62.2	−49.4	−45.0

Apheresis treatment subgroups are determined by the changes in a patients' apheresis schedule following the initiation of alirocumab.
LDL-C, low-density lipoprotein cholesterol; SD, standard deviation.

Table 4 LDL-C levels before and after apheresis or alirocumab treatment according to alirocumab dose subgroup

	Alirocumab 150 mg Q2W (n = 18)		Alirocumab 75 mg Q2W (n = 7)	
Time of level	Mean LDL-C, mg/dL [SD]	Change, %	Mean LDL-C, mg/dL [SD]	Change, %
Pre-apheresis	224.7 [70.5]		232.6 [69.2]	
Post-apheresis	95.9 [55.1]	−57.3	71.6 [39.6]	−68.2
Pre-alirocumab	202.9 [68.7]		214.6 [68.0]	
Post-alirocumab	90.2 [51.8]	−56.6	104.4 [65.3]	−52.7

LDL-C, low-density lipoprotein cholesterol; Q2W, every 2 wk; SD, standard deviation.

reduction of LDL-C at the time of apheresis with a rise in LDL-C in the period between treatments.[9,19]

A limitation of this study is the small number of patients. In addition, the data were collected retrospectively from different apheresis clinics, which may have clinic-specific differences in standard apheresis procedures, including the collection of data, and may be influenced by the clinical judgment of individual physicians, as well as patient preference. Pre- and post-apheresis values for LDL-C and other lipid markers were not collected by all apheresis clinics.

In conclusion, periodically administered apheresis has been an effective means of lowering serum lipids in patients with high cardiovascular risk. This retrospective study reflected real-world experience with alirocumab in patients with HeFH being treated at apheresis centers. Following patient-clinician shared decision-making, some patients discontinued apheresis therapy despite LDL-C levels remaining above current treatment thresholds. However, alirocumab 75 mg or 150 mg Q2W may allow some patients with HeFH to discontinue or reduce the frequency of apheresis, which has a potential effect on costs, time spent with medical procedures, and quality of life.

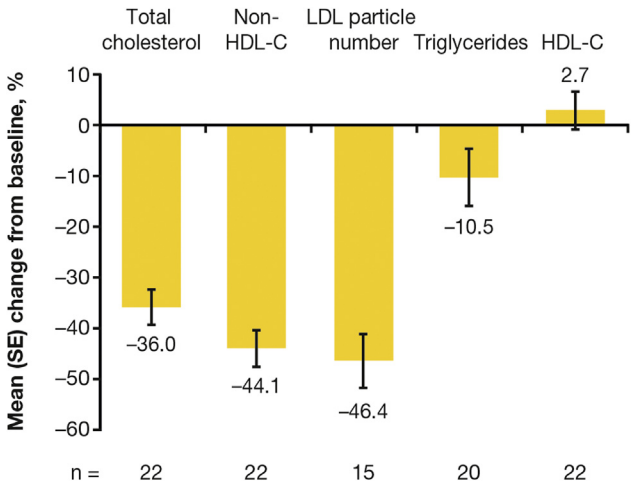

Figure 2 Percent reduction in secondary lipid parameters after alirocumab treatment. Reductions are determined using pre-apheresis lipid values. HDL-C, high-density lipoprotein cholesterol; LDL, low-density lipoprotein; non-HDL-C, non-high-density lipoprotein cholesterol; SE, standard error.

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