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Running head: Low-dose Statin plus Ezetimibe and/or Nutraceuticals in Statin-Intolerance

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Abstract

High-dose statin (HDS) therapy is recommended to reduce low-density lipoprotein cholesterol (LDL-C); however, some patients are unable to tolerate the associated side effects. Nutraceuticals have shown efficacy in lowering LDL-C. The aim of this study was to evaluate whether the combination of low-dose

statin (LDS) plus ezetimibe (EZE) or LDS plus nutraceutical (Armolipid Plus [ALP] containing red yeast rice, policosanol, and berberine) can lead to a higher proportion of high-risk patients achieving target LDL-C. A secondary objective was to assess the efficacy of triple combination LDS+EZE+ALP in resistant patients (LDL-C >70 mg/dl). A randomized, prospective, parallel-group, single-blind study was conducted in patients with coronary artery disease (CAD) (N=100) who had undergone percutaneous coronary intervention in the preceding 12 months, were HDS-intolerant, and were not at LDL-C target (<70 mg/dl) with LDS alone. Patients received either LDS+EZE or LDS+ALP. Of the 100 patients, 33 patients (66%) treated with LDS+EZE and 31 patients (62%) treated with LDS+ALP achieved target LDL-C after 3 months, which was maintained at 6 months. Patients who did not achieve the therapeutic goal received a triple combination of LDS+EZE+ALP for a further 3 months. At 6 months, 28/36 patients (78%) achieved LDL-C target. Overall, 92% of patients enrolled in this study were at target LDL-C at 6 months. No patients in any group experienced major side effects. In conclusion, in HDS-intolerant CAD patients, the combination of LDS plus EZE and/or ALP represents a valuable therapeutic option allowing most patients to reach target LDL-C within 3 to 6 months.

Keywords

coronary artery disease, ezetimibe, nutraceutical, statin-intolerance

Introduction

In patients with atherosclerotic cardiovascular disease, inadequate lipid-lowering therapy and non-adherence/intolerance to statin treatment is associated with failure to achieve target low-density lipoprotein cholesterol (LDL-C) concentration.[1,2] In such cases, other pharmacotherapy options include bile acid sequestrants, proprotein convertase subtilisin kexin 9 (PCSK9) inhibitors, and ezetimibe (EZE) in association with moderate to low dose statin (LDS) therapy. More recently, a role for nutraceuticals has

been proposed both as adjunctive and monotherapy to lower LDL-C.[3-5] The combination of red yeast rice and berberine is shown to improve the lipid profile in subjects intolerant to statins.[6,7] This nutraceutical combination (found in Armolipid Plus [ALP]) is effective in reducing total cholesterol and LDL-C concentrations and can lead to an improvement in cardiovascular risk profile.[8-10] ALP (alone or in combination with EZE) is effective in statin-intolerant patients with coronary heart disease,[11] and in combination with LDS in high-dose statin (HDS)-intolerant patients with coronary artery disease (CAD).[12] The primary objective of this study was to evaluate whether the combination of LDS plus EZE and the combination of LDS plus ALP can lead to a higher proportion of patients achieving the LDL-C target (LDL <70 mg/dl) among HDS-intolerant patients with CAD. A secondary outcome was to evaluate the efficacy of the triple combination of LDS plus EZE plus ALP in those patients resistant to the dual combinations.

Methods

This was a randomized, prospective, parallel group, single-blind trial of LDS, EZE and ALP in HDS-intolerant CAD patients (Target ChOlesterol; TACO). Patients were consecutively enrolled from October 1, 2017 until December 21, 2017 (ClinicalTrials.gov identifier: NCT03277079). The nutraceutical used in this trial was ALP a formulation of 6 naturally occurring plant extracts which contains 3 naturally occurring substances with putative complementary lipid-lowering properties: red yeast rice (200 mg, corresponding to 3 mg of monacolin), policosanol (10 mg) and berberine (500 mg), combined with 3 other ingredients folic acid (0.2 mg), astaxanthin (0.5 mg), and coenzyme Q10 (2 mg) (Mylan; manufactured as per European Union Good Manufacturing Practice requirements and available in several European and Asian countries). The study was carried out during routine clinical practice at the IRCCS San Raffaele Pisana, Rome, Italy, in accordance with international guidelines and in line with the principles outlined in the Declaration of Helsinki. Ethical Committee approval and patients' written consent were obtained.

Eligible participants were 1) those with CAD who underwent percutaneous coronary intervention (PCI) in the preceding 12 months; 2) were intolerant to HDS; and 3) who did not achieve LDL-C target (<70 mg/dl) after treatment with LDS. HDS intolerance was defined as: myalgia (i.e. muscle complaints without serum creatine kinase elevations) and/or myositis (i.e. muscle symptoms with creatine kinase elevations) and/or rhabdomyolysis (i.e. creatine kinase levels >10 times the upper limit of normal with an elevated creatinine level consistent with pigment-induced nephropathy) and/or gastrointestinal disorders (i.e. alanine aminotransferase or aspartate aminotransferase >2 times the upper limit of normal). HDS was defined as: atorvastatin, lovastatin, simvastatin and pravastatin at doses >20 mg, and rosuvastatin at a dose >10 mg.

Exclusion criteria included: glomerular filtration rate of <30 mUmin/1.73 m^2 (based on creatinine measured at the screening visit and calculated by a standard formula) and creatine kinase or alanine aminotransferase or aspartate aminotransferase above normal measured at the screening visit.

One hundred patients were randomized (1:1) to receive LDS (20 mg/day atorvastatin, or 20 mg/day simvastatin, or 5 to 10 mg/day rosuvastatin) plus either EZE (10 mg/day) or ALP (1 tablet/day). After 3 months, the patients who reached target LDL-C <70 mg/dl continued with the dual combination therapy for a further 3 months. Patients from either group who did not achieve the therapeutic goal were invited to receive a triple combination of LDS+EZE+ALP for a further 3 months. At the baseline visit, efficacy and safety investigations were performed, including physical examination, vital sign assessment, and laboratory blood tests (LDL-C, high-density lipoprotein cholesterol [HDL-C], total cholesterol, triglycerides, transaminases and creatine kinase). All examinations were repeated at the 3-month and 6-month follow-up visits.

The primary outcome was the proportion of patients who achieved the therapeutic target for LDL-C (<70 mg/dl) after 3 months treatment with dual combination therapy. A secondary outcome in patients who did not achieve therapeutic target at 3 months, was the proportion of patients who achieved the

therapeutic target for LDL-C after 3 months treatment with the triple combination of LDS+EZE+ALP (months 3 to 6). Other outcomes were the effects on lipid profile: changes in total cholesterol, triglycerides, LDL-C and HDL-C at 3 and 6 months, and treatment tolerability. In the event of an adverse event, subjects were counselled to stop taking the medicine permanently or temporarily.

Data for continuous variables were expressed as mean values and standard deviation. Categorical data were expressed as number of patients and percentage. The Kolmogorov–Smirnov test for goodness of adaptation was used to verify distribution normality. Based on the results of the Kolmogorov–Smirnov test, statistical transformations were applied if needed. Baseline characteristics between groups at the start of the treatment were compared using the Student t Test for independent samples or chi-square test. Analyses of treatment intragroup associated changes were performed using a series of repeated measures analysis of variance. A p-value <0.05 was considered as statistically significant for all tests.

Results

One hundred patients with CAD were enrolled consecutively in the study (mean age 61 years; 55% male), among whom 30% had an acute coronary syndrome. Patients were treated with LDS and randomized to receive either EZE or ALP. Baseline clinical features and lipid profiles were similar between groups (Table 1).

The statin therapies most frequently taken by patients were simvastatin 20 mg and atorvastatin 20 mg (Table 2). The flow of patients through the study is presented in Figure 1.

After 3 months, 33 (66%) of those who received LDS+EZE and 31 (62%) who received LDS+ALP achieved the therapeutic target for LDL-C (<70 mg/dl) and maintained this result at 6 months (Figure 1). Greater reductions in LDL-C concentration were observed in the LDS+ALP group (–26 mg/dl) as compared with the LDS+EZE group (–16 mg/dl) at 3 months (p <0.00001) (Table 3) (Figure 2A). Significantly greater reductions in total cholesterol were found in the LDS+ALP group vs. LDS+EZE; while

comparable effects on HDL-C and triglycerides were found for the 2 groups, with a trend for greater reduction in triglycerides with LDS+ALP that approached significance (p = 0.073) (Table 3).

At the 3-month visit, the remaining 36 resistant patients (defined as LDL-C >70mg/dl) from both treatment groups (n = 19 from the LDS+ALP group and n = 17 from the LDS+EZE group) were invited to take the triple combination of LDS+EZE+ALP for a further 3 months. At the 6-month visit, 28 of the 36 (78%) on triple therapy achieved the therapeutic target (n = 16 from the LDS+ALP group and n = 12 from the LDS+EZE group), with a mean LDL-C of 69 mg/dl (Figure 1). The mean reduction in LDL-C concentration from baseline at 6 months was –33 mg/dl (Table 4) (Figure 2B). Significant changes from baseline in total cholesterol, LDL-C and triglyceride concentration were measured at 6 months (p <0.0006), with a modest increase in HDL-C (Table 4). Overall, 64% and 92% of patients enrolled into this study achieved the LDL-C therapeutic target at month 3 and 6, respectively. After 6 months of therapy, only 8% of patients (n = 8) remained with LDL-C concentration above target (mean LDL-C = 77.5 mg/dl).

The triple combination was well tolerated and no patients (in all groups) experienced side effects. No significant differences were recorded between the two groups for laboratory safety variables including transaminases and creatine kinase.

Discussion

In this study, we assessed the effects of the nutraceutical combination ALP and EZE in addition to LDS therapy in patients with CAD and prior PCI. We found that dual therapy with either LDS plus EZE or ALP allowed more than 60% of patients to achieve the therapeutic target for lowering LDL-C concentration (<70 mg/dl) by 3 months (66% and 62%, respectively). While there was no significant difference between groups for the proportion of patients who achieved target LDL-C at 3 months, LDS+ALP was significantly more effective in terms of change from baseline in total cholesterol and LDL-C concentration at 3 months (p <0.0004). Moreover, among patients who did not achieve target LDL-C at 3 months (n=36), administration of the triple combination of LDS+EZE+ALP enabled 77% of these 36

patients to achieve target LDL-C concentration at 6 months. Overall, 92% of patients who entered our trial were able to reach the desired LDL-C target set by the 2016 European Society of Cardiology (ESC)/European Atherosclerosis Society (EAS) guidelines for the management of dyslipidemia, which recommend the use of nutraceuticals as an alternative or in addition to lipid-lowering drugs.[3]

Our findings are consistent with previous reports in other patient populations.[13-15] In our study, LDS+EZE resulted in a 17% reduction in LDL-C concentration at 3 months. A prior meta-analysis of 8 RCTs showed that EZE was associated with a significant mean reduction in LDL-C from baseline to 12 weeks compared with placebo (–19%; p <0.00001).[16] In our earlier study of HDS-intolerant patients with CAD who had undergone PCI, 70% of patients who received LDS+ALP achieved the therapeutic target of LDL-C <70 mg/dl at 3 months.[12] Also, in a study of patients with dyslipidemia, coronary heart disease and prior PCI who were statin intolerant, ALP alone or in addition to EZE improved the lipid profile and allowed nearly 75% of patients to achieve the therapeutic target (LDL-C <100 mg/dl) at 12 months.[11]

A meta-analysis of ALP versus control or active interventions has measured the effect of the ALP on lipid concentration as weighted mean differences as follows: total cholesterol (−26.15 mg/dl; p <0.001), LDL-C (−23.85 mg/dl; p <0.001), HDL-C (+2.53 mg/dl; p <0.001), and triglycerides (−13.83 mg/dl; p <0.001).[10] In this study, a greater reduction in LDL-C concentration was achieved with the LDS+ALP than with LDS+EZE at 3 months (–26 mg/dl versus –16 mg/dl, respectively). In a study of HDS-intolerant patients who did not achieve their therapeutic target with EZE, the combination of ALP+EZE achieved a further percentage decrease in LDL-C concentration of 14%.[7]

This is consistent with the outcomes of previous trials of ALP versus EZE,[7,11] and may be expected as ALP contains a combination of nutraceuticals including 3 lipid-lowering compounds, policosanol, red yeast rice, and berberine, with synergistic mechanisms of action. Red yeast rice and policosanol target the HMG-CoA enzyme reducing cholesterol synthesis (the active ingredient of red yeast rice, monacolin K [lovastatin], inhibits HMG-CoA reductase activity competitively, whereas polycosanol decreases HMG-

CoA reductase synthesis) and berberine, amongst other activities, reduces PCSK9 expression which reduces LDL receptor degradation and increases LDL-C liver uptake.[8,17-22] EZE inhibits intestinal uptake of dietary and biliary cholesterol without affecting the absorption of fat-soluble nutrients. In this way, EZE reduces the amount of cholesterol delivered to the liver, which responds by upregulating LDL receptor expression, and in turn leads to increased clearance of LDL-C from the blood.[3]

In our study, ALP was added to a statin at low dose, with complementary actions on lipid concentration. Statins reduce the synthesis of cholesterol in the liver by competitive inhibition of the enzyme HMG-CoA reductase. The reduction in intracellular cholesterol concentration induces an increased expression of LDL receptor on the surface of the hepatocytes, which results in increased uptake of LDL-C from the blood and a decreased plasma concentration of LDL-C and other apoB-containing lipoproteins, including triglyceride-rich particles.[3]

Possible pleiotropic effects have been shown to occur with HDS in patients with recent PCI or ACS (attenuation of inflammatory endothelial response and adhesion molecules expression) that could improve long-term outcomes.[23] Since ALP contains only 3 mg of a low potency statin (lovastatin), it was considered unlikely that such effects may occur; therefore, the related parameters (inflammatory endothelial response, adhesion molecules expression) were not tested in the present study.

In contrast, additional risks have been identified with the use of HDS, including kidney injury, musculoskeletal disease, diabetes mellitus and a possible link to Parkinson's disease, which should be taken into consideration for long-term management of dyslipidemias.[24-26] All treatments in our trial were well tolerated, which is consistent with our previous trial results.[11-13] To date, data on over 1600 patients treated with Armolipid Plus have been published from studies ranging from 6 to 48 weeks in which very few adverse events have been reported (2.2%), the most common of which was constipation (n = 8).[8]

Interpretation of our study results is limited by the relatively small study size, the collection only of surrogate variables, i.e. lipid profiles, and the inadequacy of current definitions of statin intolerance.[27] The use of surrogate markers makes the result with modest power, instead of clinical driven purpose.

Nonetheless, our study demonstrates that there are alternative treatment strategies available to high cardiovascular risk patients who are intolerant to statin therapy at high doses, that will enable them to reach the stringent therapeutic targets set out by the ESC/EAS recommendations.[3] In addition, the ESC/EAS guidelines recommend the use of LDS in patients at increased risk of adverse effects with high-intensity statins including older patients, and those with hepatic impairment, renal impairment or potential for interaction with essential concomitant therapy. EZE or other lipid-lowering therapies may be added to LDS to maximise LDL-C reduction. The various combinations of LDS, EZE and ALP tested in our study provide a high degree of cholesterol control while maintaining a good tolerability profile. Our results add to the available evidence attesting to the utility of nutraceuticals in control of cardiovascular risk factors and will support future guideline updates to reinforce the place of nutraceuticals in the therapeutic armamentarium.

In conclusion, these results show that in patients with CAD who are HDS-intolerant, treatment with LDS and either EZE or ALP represents a reliable, effective and safe treatment option. Furthermore, among patients who are initially resistant to dual therapy, the triple combination of LDS+EZE+ALP can allow the majority of patients to achieve therapeutic LDL-C target within 6 months.

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Disclosures

The authors have no conflicts of interest to disclose.

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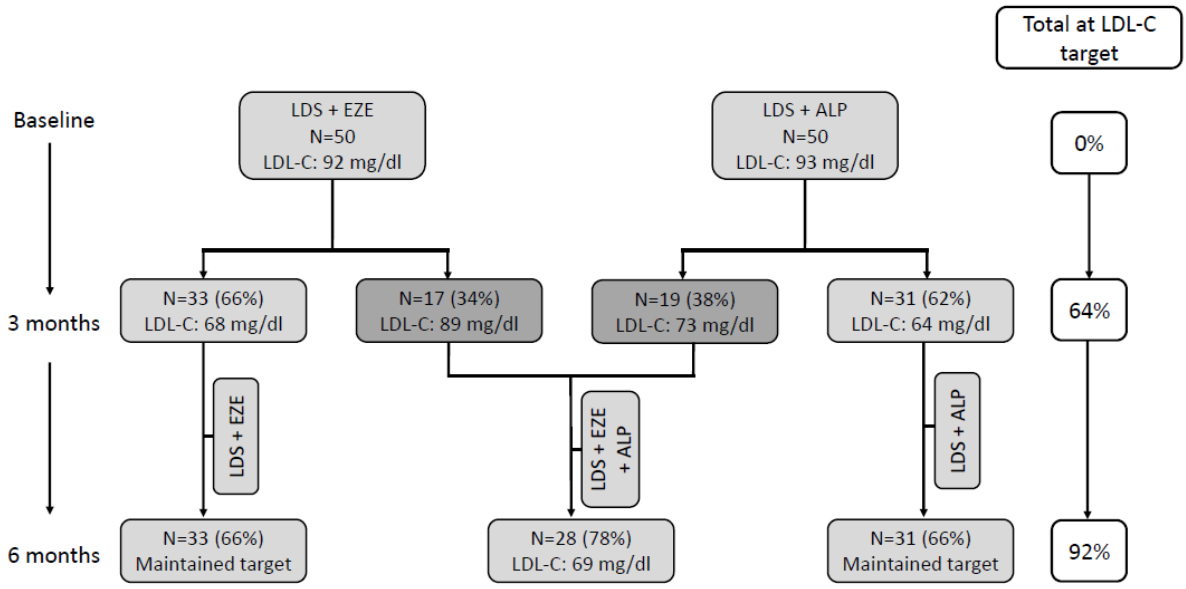

Figure 1 Overall proportion of patients who achieved the therapeutic target (low density lipoprotein-cholesterol [LDL-C] <70 mg/dl) with dual combination therapy at 3 months, and dual or triple combination therapy at 6 months.

Dual combination therapy with either low dose statin (LDS) plus ezetimibe (EZE) (n=50) or LDS plus nutraceutical (Armolipid Plus [ALP]) (n=50) for 3 months followed by either continuation on dual therapy (n=64) or triple therapy with LDS+EZE+ALP (n=36).

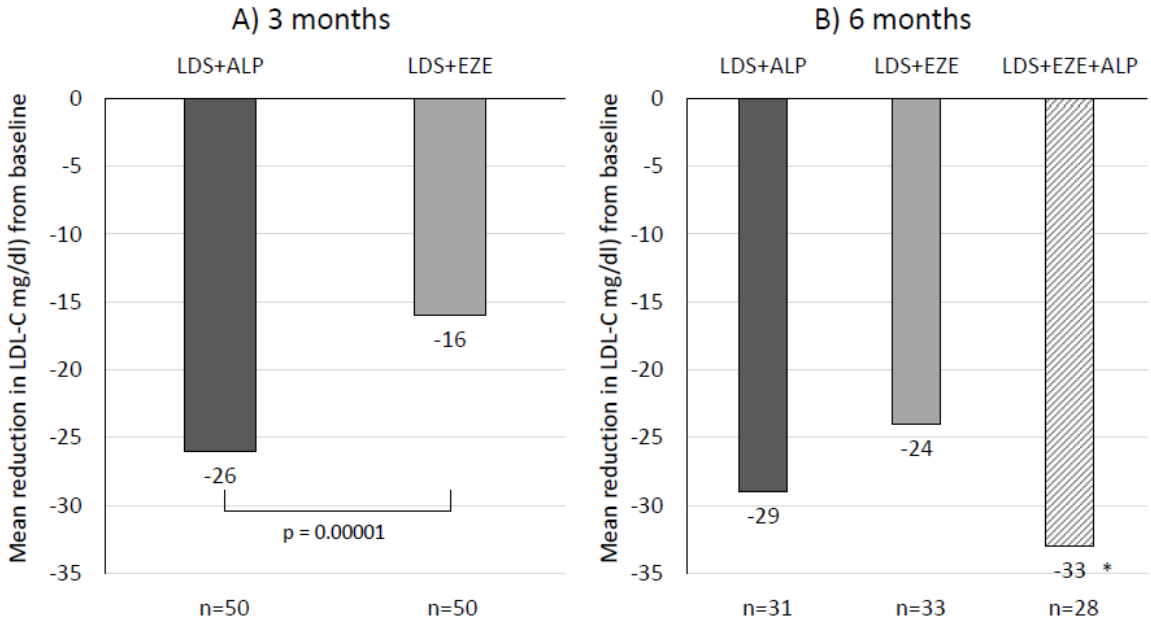

Figure 2 Mean reduction in LDL-C (mg/dl) from baseline to A) 3 months and B) 6 months with dual and triple combination therapy.

* p = 0.00001 for change from baseline; ALP, Armolipid Plus (nutraceutical); EZE, ezetimibe; LDS, low density statin; LDL-C, low density lipoprotein-cholesterol.

Table 1

Baseline characteristics in the 2 treatment groups

Variable[†]	Low-dose statin plus ezetimibe (n=50)	Low-dose statin plus nutraceutical (n=50)
Men	28 (56%)	27 (54%)
Age (years), mean ±SD	60 ±7	61 ±8
Diabetes mellitus	13 (26%)	12 (24%)
Hypertension	19 (38%)	20 (40%)
Current smoker	4 (8%)	5 (10%)
Total cholesterol (mg/dl), mean ±SD	167 ±14	168 ±16
Low-density lipoprotein cholesterol (mg/dl), mean ±SD	92 ±11	93 ±10
High-density lipoprotein cholesterol (mg/dl), mean ±SD	47 ±8	47 ±12
Triglycerides (mg/dl), mean ±SD	137 ±25	136 ±28
Left ventricular ejection fraction (%)	58 ±4	58 ±3
Blood creatinine (mg/dl), mean ±SD	0.9 ±0.2	0.9 ±0.3

[†] p = non-significant for all between group comparisons.

SD, standard deviation.

Table 2

Treatment comparison between groups

Baseline therapies	Low-dose statin plus ezetimibe (n=50)	Low-dose statin plus nutraceutical (n=50)
Statin therapy[†]		
Atorvastatin 20 mg	18 (36%)	17 (34%)
Simvastatin 20 mg	21 (42%)	20 (40%)
Rosuvastatin 10 mg	8 (16%)	9 (18%)
Rosuvastatin 5 mg	3 (6%)	4 (8%)
Other concomitant therapies[†]		
Aspirin	50 (100%)	50 (100%)
Platelet inhibitors[‡]	50 (100%)	50 (100%)
Beta-blockers	46 (92%)	47 (94%)
ACE inhibitor/ARB	48 (96%)	47 (94%)

[†] p = non-significant for all between group comparisons; [‡] $P2Y_{12}$ inhibitors: clopidogrel, prasugrel, ticagrelor.

ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker.

Table 3

Changes in lipid concentrations from baseline to 3 months of therapy, following treatment with low-dose statin plus ezetimibe versus low-dose statin plus nutraceutical combination

Variable	Low-dose statin plus ezetimibe combination (n=50)			Low-dose statin plus nutraceutical combination (n=50)			p-value[†]
	Baseline, mean ±SD	3 months, mean ±SD	% change	Baseline, mean ±SD	3 months, mean ±SD	% change	
Total cholesterol (mg/dl)	167 ±14	151 ±14	–10%	168 ±16	141 ±14	–16%	0.0005
LDL-C (mg/dl)	92 ±11	76 ±11	–17%	93 ±10	67 ±6	–28%	0.00001
HDL-C (mg/dl)	47 ±8	49 ±7	+4%	47 ±12	49 ±12	+4%	0.9367
Triglycerides (mg/dl)	137 ±25	131 ±22	–4%	136 ±28	123 ±24	–10%	0.0730

[†] The p-value is for the between group comparisons.

HDL-C, High-density lipoprotein-cholesterol; LDL-C, low density lipoprotein-cholesterol; SD, standard deviation.

Table 4

Changes in lipid concentrations from baseline to 6 months of therapy, after dual therapy for 3 months, followed by triple therapy with low-dose statin plus ezetimibe plus nutraceutical for a further 3 months

Variable	Dual therapy[‡] for 3 months followed by triple therapy with LDS+EZE+ALP for 3 months (n=36)				p-value[†]
	Baseline, mean ±SD	3 months, mean ±SD	6 months, mean ±SD	% change from baseline to 6 months	
Total cholesterol (mg/dl)	174 ±4	152 ±25	141 ±14	–19%	0.00001
LDL-C (mg/dl)	102 ±8	81 ±13	69 ±2	–32%	0.00001
HDL-C (mg/dl)	44 ±6	46 ±6	47 ±6	+7%	0.1404
Triglycerides (mg/dl)	139 ±30	127 ±30	119 ±29	–14%	0.0006

[†] The p-value is for change from baseline; [‡] Dual therapy with either low dose statin (LDS) plus ezetimibe (EZE) or LDS plus nutraceutical (Armolipid Plus [ALP]).

HDL-C, High-density lipoprotein-cholesterol; LDL-C, low density lipoprotein-cholesterol; SD, standard deviation.