

## Accepted Manuscript

## Usefulness of Low Dose Statin Plus Ezetimibe and/or Nutraceuticals in Patients With Coronary Artery Disease Intolerant to High-Dose Statin Treatment

Giuseppe Marazzi MD, PhD , Giuseppe Campolongo MD ,  
 Francesco Pelliccia MD, PhD , Paolo Calabrò , Luca Cacciotti MD ,  
 Cristiana Vitale MD, PhD , Rosalba Massaro MD ,  
 Maurizio Volterrani MD, PhD , Giuseppe Rosano MD, PhD

PII: S0002-9149(18)31970-2  
 DOI: <https://doi.org/10.1016/j.amjcard.2018.09.041>  
 Reference: AJC 23580

To appear in: *The American Journal of Cardiology*

Received date: 2 July 2018  
 Revised date: 19 September 2018

Please cite this article as: Giuseppe Marazzi MD, PhD , Giuseppe Campolongo MD ,  
 Francesco Pelliccia MD, PhD , Paolo Calabrò , Luca Cacciotti MD , Cristiana Vitale MD, PhD ,  
 Rosalba Massaro MD , Maurizio Volterrani MD, PhD , Giuseppe Rosano MD, PhD , Usefulness  
 of Low Dose Statin Plus Ezetimibe and/or Nutraceuticals in Patients With Coronary Artery Dis-  
 ease Intolerant to High-Dose Statin Treatment, *The American Journal of Cardiology* (2018), doi:  
<https://doi.org/10.1016/j.amjcard.2018.09.041>

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.



AJC-D-18-01812 R1

**Usefulness of Low Dose Statin Plus Ezetimibe and/or Nutraceuticals in Patients With Coronary Artery Disease Intolerant to High-Dose Statin Treatment**

Giuseppe Marazzi, MD, PhD<sup>a,\*</sup>, Giuseppe Campolongo, MD<sup>a</sup>, Francesco Pelliccia, MD, PhD<sup>b</sup>, Paolo Calabrò<sup>c</sup>, Luca Cacciotti, MD<sup>d</sup>, Cristiana Vitale, MD, PhD<sup>a,e</sup>, Rosalba Massaro MD<sup>a</sup>, Maurizio Volterrani, MD, PhD<sup>a</sup>, Giuseppe Rosano, MD, PhD<sup>a,e</sup>

<sup>a</sup>Instituto di Ricerca a Carattere Scientifico (IRCCS) San Raffaele, Rome, Italy; <sup>b</sup>University of Rome "la Sapienza", Rome, Italy; University of Campania, L. Vanvitelli, Caserta, Italy; <sup>d</sup>Institute of Cardiology, Madre Giuseppina Vannini Hospital, Rome, Italy; <sup>e</sup>St George's Hospital NHS Trust Medical School, London, UK

\*Corresponding author: Tel: (3906) 5225-1; fax: (3906) 99322931. E-mail address: giuseppe.marazzi@sanraffaele.it (G. Marazzi).

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

TRIAL REGISTRATION: clinicaltrials.gov identifier: NCT03277079

**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 (Armoliplus 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.<sup>1,2</sup> 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.<sup>3-5</sup> The combination of red yeast rice and berberine is shown to improve the lipid profile in subjects intolerant to statins.<sup>6,7</sup> 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.<sup>8-10</sup> ALP (alone or in combination with EZE) is effective in statin-intolerant patients with coronary heart disease,<sup>11</sup> and in combination with LDS in high-dose statin (HDS)-intolerant patients with coronary artery disease (CAD).<sup>12</sup> 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 mL/min/1.73 m<sup>2</sup> (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  $>70$ mg/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.<sup>3</sup>

Our findings are consistent with previous reports in other patient populations.<sup>13-15</sup> 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 ( $-19\%$ ;  $p < 0.00001$ ).<sup>16</sup> 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.<sup>12</sup> 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.<sup>11</sup>

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;  $p < 0.001$ ).<sup>10</sup> 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%.<sup>7</sup>

This is consistent with the outcomes of previous trials of ALP versus EZE,<sup>7,11</sup> 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 policosanol decreases HMG-



CoA reductase synthesis) and berberine, amongst other activities, reduces PCSK9 expression which reduces LDL receptor degradation and increases LDL-C liver uptake.<sup>8,17-22</sup> 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.<sup>3</sup>

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.<sup>3</sup>

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.<sup>23</sup> 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.<sup>24-26</sup> All treatments in our trial were well tolerated, which is consistent with our previous trial results.<sup>11-13</sup> 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).<sup>8</sup>

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.<sup>27</sup> 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.<sup>3</sup> 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.

### **Acknowledgements**

This work was supported by the Italian Ministry of Education, University and Research. The National Operational Program (PON) for Research and Competitiveness is co-funded with the European Regional Development Fund (ERDF) and national resources. It promotes initiatives and projects for scientific research and industrial competitiveness.

**Disclosures**

The authors have no conflicts of interest to disclose.

1. Parris ES, Lawrence DB, Mohn LA, Long LB. Adherence to statin therapy and LDL cholesterol goal attainment by patients with diabetes and dyslipidemia. *Diabetes Care* 2005;28:595–599.
2. Pirro M, Del Giorno R, Lupattelli G, Mannarino MR, Roscini AR, Covelli D, Schillaci G, Pasqualini L, Bagaglia F, Siepi D, Mannarino E. Cardiovascular risk factors and recommended lipid goals attainment among patients referred in a tertiary care lipid clinic. *Eur J Intern Med* 2011;22:412–417.
3. Catapano AL, Graham I, De Backer G, Wiklund O, Chapman MJ, Drexel H, Hoes AW, Jennings CS, Landmesser U, Pedersen TR, Reiner Z, Riccardi G, Taskinen MR, Tokgozoglul, Verschuren WM, Vlachopoulos C, Wood DA, Zamorano JL, Authors/Task Force Members. 2016 ESC/EAS Guidelines for the Management of Dyslipidaemias: the task force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS) developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). *Eur Heart J* 2016;37:2999–3058.
4. Ward NC, Pang J, Ryan JDM, Watts GF. Nutraceuticals in the management of patients with statin-associated muscle symptoms, with a note on real-world experience. *Clin Cardiol* 2018;41:159–165.
5. Ward N, Sahebkar A, Banach M, Watts G. Recent perspectives on the role of nutraceuticals as cholesterol-lowering agents. *Curr Opin Lipidol* 2017;28:495–501.
6. Cicero AF, Derosa G, Bove M, Imola F, Borgi C, Gaddi AV. Long-term effectiveness and safety of a nutraceutical based approach to reduce cholesterolemia in statin intolerant subjects with and without metabolic syndrome. *Curr Top Nutraceutical Res* 2009;7:121–126.

7. Pisciotta L, Bellocchio A, Bertolini S. Nutraceutical pill containing berberine versus ezetimibe on plasma lipid pattern in hypercholesterolemic subjects and its additive effect in patients with familial hypercholesterolemia on stable cholesterol-lowering treatment. *Lipids Health Dis* 2012;11:123.
8. Barrios V, Escobar C, Cicero AFG, Burke D, Fasching P, Banach M, Bruckert E. A nutraceutical approach (Armolid Plus) to reduce total and LDL cholesterol in individuals with mild to moderate dyslipidemia: Review of the clinical evidence. *Atheroscler Suppl* 2017;24:1–15.
9. Izzo R, de Simone G, Giudice R, Chinali M, Trimarco V, De Luca N, Trimarco B. Effects of nutraceuticals on prevalence of metabolic syndrome and on calculated Framingham Risk Score in individuals with dyslipidemia. *J Hypertens* 2010;28:1482–1487.
10. Pirro M, Mannarino MR, Bianconi V, Simental-Mendia LE, Bagaglia F, Mannarino E, Sahebkar A. The effects of a nutraceutical combination on plasma lipids and glucose: A systematic review and meta-analysis of randomized controlled trials. *Pharmacol Res* 2016;110:76–88.
11. Marazzi G, Pelliccia F, Campolongo G, Quattrino S, Cacciotti L, Volterrani M, Gaudio C, Rosano G. Usefulness of Nutraceuticals (Armolid Plus) Versus Ezetimibe and Combination in Statin-Intolerant Patients With Dyslipidemia With Coronary Heart Disease. *Am J Cardiol* 2015;116:1798–1801.
12. Marazzi G, Campolongo G, Pelliccia F, Quattrino S, Vitale C, Cacciotti L, Massaro R, Volterrani M, Rosano G. Comparison of low-dose statin versus low-dose statin + armolid plus in high-intensity statin-intolerant patients with a previous coronary event and percutaneous coronary intervention (ADHERENCE Trial). *Am J Cardiol* 2017;120:893–897.
13. Marazzi G, Cacciotti L, Pelliccia F, Iaia L, Volterrani M, Caminiti G, Sposato B, Massaro R, Grieco F, Rosano G. Long-term effects of nutraceuticals (berberine, red yeast rice, policosanol) in elderly hypercholesterolemic patients. *Adv Ther* 2011;28:1105–1113.

14. Affuso F, Ruvolo A, Micillo F, Sacca L, Fazio S. Effects of a nutraceutical combination (berberine, red yeast rice and policosanols) on lipid levels and endothelial function randomized, double-blind, placebo-controlled study. *Nutr Metab Cardiovasc Dis* 2010;20:656–661.
15. Sola R, Valls RM, Puzo J, Calabuig JR, Brea A, Pedret A, Morina D, Villar J, Millan J, Anguera A. Effects of poly-bioactive compounds on lipid profile and body weight in a moderately hypercholesterolemic population with low cardiovascular disease risk: a multicenter randomized trial. *PLoS One* 2014;9:e101978.
16. Pandor A, Ara RM, Tumor I, Wilkinson AJ, Paisley S, Duenas A, Durrington PN, Chilcott J. Ezetimibe monotherapy for cholesterol lowering in 2,722 people: systematic review and meta-analysis of randomized controlled trials. *J Intern Med* 2009;265:568–580.
17. Endo A. Chemistry, biochemistry, and pharmacology of HMG-CoA reductase inhibitors. *Klin Wochenschr* 1988;66:421–427.
18. Menendez R, Amor AM, Rodeiro I, Gonzalez RM, Gonzalez PC, Alfonso JL, Mas R. Policosanol modulates HMG-CoA reductase activity in cultured fibroblasts. *Arch Med Res* 2001;32:8–12.
19. Monograph. Policosanol. *Altern Med Rev* 2004;9:312–317.
20. Cameron J, Ranheim T, Kulseth MA, Leren TP, Berge KE. Berberine decreases PCSK9 expression in HepG2 cells. *Atherosclerosis* 2008;201:266–273.
21. Kong W, Wei J, Abidi P, Lin M, Inaba S, Li C, Wang Y, Wang Z, Si S, Pan H, Wang S, Wu J, Wang Y, Li Z, Liu J, Jiang JD. Berberine is a novel cholesterol-lowering drug working through a unique mechanism distinct from statins. *Nat Med* 2004;10:1344–1351.
22. Doggrell SA. Berberine - a novel approach to cholesterol lowering. *Expert Opin Investig Drugs* 2005;14:683–685.
23. Guarinin G, Marzilli M. Defining the role of high-dose statins in PCI. *Am J Cardiovasc Drugs* 2013;13:189–197.

24. Mansi IA, Mortensen EM, Pugh MJ, Wegner M, Frei CR. Incidence of musculoskeletal and neoplastic diseases in patients on statin therapy: results of a retrospective cohort analysis. *Am J Med Sci* 2013;345:343–348.
25. Dormuth CR, Filion KB, Paterson JM, James MT, Teare GF, Raymond CB, Rahme E, Tamim H, Lipscombe L, Canadian Network for Observational Drug Effect Studies I. Higher potency statins and the risk of new diabetes: multicentre, observational study of administrative databases. *BMJ* 2014;348:g3244.
26. Huang X, Alonso A, Guo X, Umbach DM, Lichtenstein ML, Ballantyne CM, Mailman RB, Mosley TH, Chen H. Statins, plasma cholesterol, and risk of Parkinson's disease: a prospective study. *Mov Disord* 2015;30:552–559.
27. Banach M, Rizzo M, Toth PP, Farnier M, Davidson MH, Al-Rasadi K, Aronow WS, Athyros V, Djuric DM, Ezhov MV, Greenfield RS, Hovingh GK, Kostner K, Serban C, Lighezan D, Fras Z, Moriarty PM, Muntner P, Goudev A, Ceska R, Nicholls SJ, Broncel M, Nikolic D, Pella D, Puri R, Rysz J, Wong ND, Bajnok L, Jones SR, Ray KK, Mikhailidis DP. Statin intolerance - an attempt at a unified definition. Position paper from an International Lipid Expert Panel. *Arch Med Sci* 2015;11:1–23.

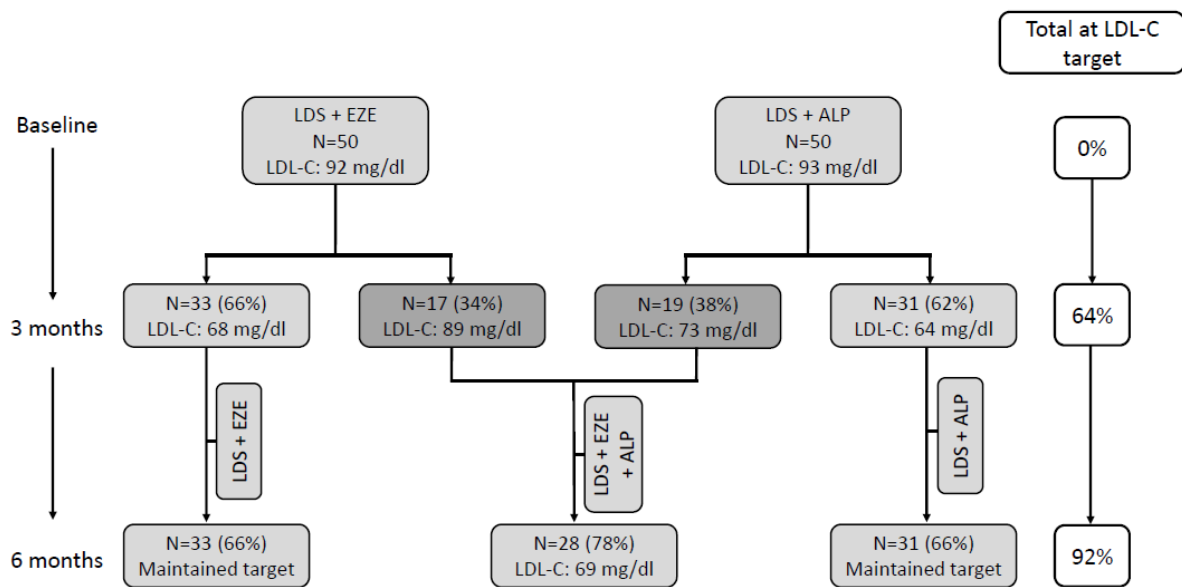


Figure 1 Overall proportion of patients who achieved the therapeutic target (low density lipoprotein-cholesterol [LDL-C] <70 mg/dl) with dual combination therapy at 3 months, and dual or triple combination therapy at 6 months.

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).

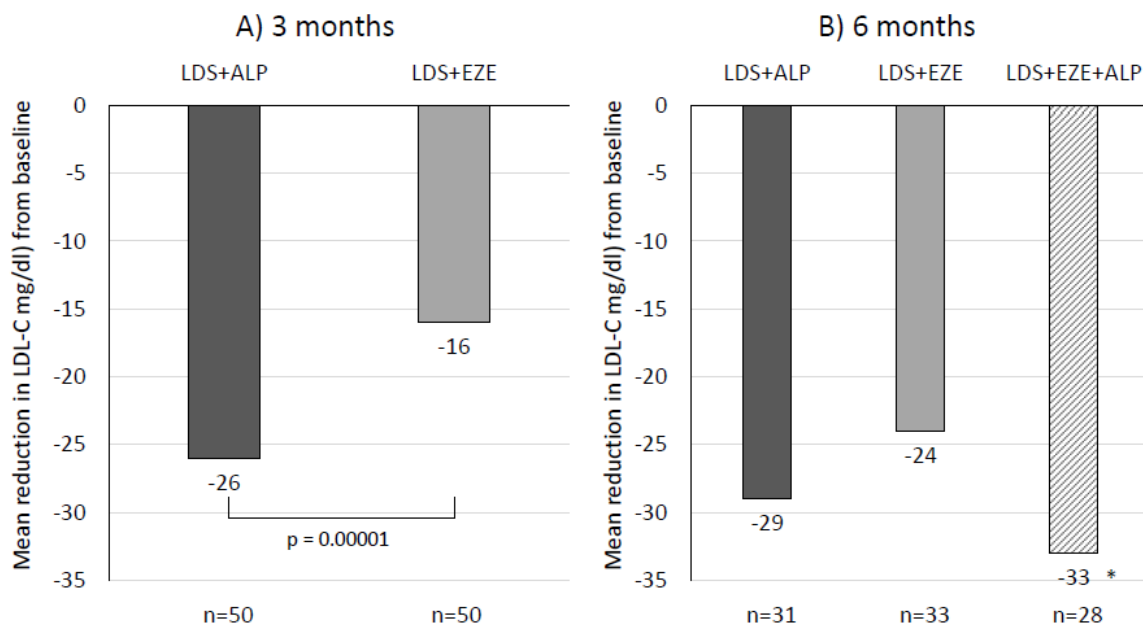


Figure 2 Mean reduction in LDL-C (mg/dl) from baseline to A) 3 months and B) 6 months with dual and triple combination therapy.

\*  $p = 0.00001$  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 <sup>†</sup>                                       | Low-dose statin<br>plus ezetimibe<br>(n=50) | Low-dose statin<br>plus nutraceutical<br>(n=50) |
|-------------------------------------------------------------|---------------------------------------------|-------------------------------------------------|
| Men                                                         | 28 (56%)                                    | 27 (54%)                                        |
| Age (years), mean $\pm$ SD                                  | 60 $\pm$ 7                                  | 61 $\pm$ 8                                      |
| Diabetes mellitus                                           | 13 (26%)                                    | 12 (24%)                                        |
| Hypertension                                                | 19 (38%)                                    | 20 (40%)                                        |
| Current smoker                                              | 4 (8%)                                      | 5 (10%)                                         |
| Total cholesterol (mg/dl), mean $\pm$ SD                    | 167 $\pm$ 14                                | 168 $\pm$ 16                                    |
| Low-density lipoprotein cholesterol (mg/dl), mean $\pm$ SD  | 92 $\pm$ 11                                 | 93 $\pm$ 10                                     |
| High-density lipoprotein cholesterol (mg/dl), mean $\pm$ SD | 47 $\pm$ 8                                  | 47 $\pm$ 12                                     |
| Triglycerides (mg/dl), mean $\pm$ SD                        | 137 $\pm$ 25                                | 136 $\pm$ 28                                    |
| Left ventricular ejection fraction (%)                      | 58 $\pm$ 4                                  | 58 $\pm$ 3                                      |
| Blood creatinine (mg/dl), mean $\pm$ SD                     | 0.9 $\pm$ 0.2                               | 0.9 $\pm$ 0.3                                   |

<sup>†</sup> p = non-significant for all between group comparisons.

SD, standard deviation.

Table 2

Treatment comparison between groups

| Baseline therapies                             | Low-dose statin plus<br>ezetimibe (n=50) | Low-dose statin plus<br>nutraceutical (n=50) |
|------------------------------------------------|------------------------------------------|----------------------------------------------|
| <i>Statin therapy<sup>†</sup></i>              |                                          |                                              |
| 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%)                                       |
| <i>Other concomitant therapies<sup>†</sup></i> |                                          |                                              |
| Aspirin                                        | 50 (100%)                                | 50 (100%)                                    |
| Platelet inhibitors <sup>‡</sup>               | 50 (100%)                                | 50 (100%)                                    |
| Beta-blockers                                  | 46 (92%)                                 | 47 (94%)                                     |
| ACE inhibitor/ARB                              | 48 (96%)                                 | 47 (94%)                                     |

<sup>†</sup> p = non-significant for all between group comparisons; <sup>‡</sup> P2Y<sub>12</sub> 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 <sup>†</sup> |
|---------------------------|---------------------------------------------------|--------------------|----------|-------------------------------------------------------|--------------------|----------|----------------------|
|                           | 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               |

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

<sup>†</sup> The p-value is for change from baseline; <sup>‡</sup> 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.