Add-on ezetimibe reduces small dense LDL cholesterol levels without affecting absorption of eicosapentaenoic acid in patients with coronary artery disease: a pilot study

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Abstract

Background: Residual risk of cardiovascular disease from increased small dense low-density lipoprotein (sdLDL)-cholesterol and *n*-3 polyunsaturated fatty acid (PUFA) levels are a considerable therapeutic issue. The purpose of this study was to evaluate the effect of ezetimibe as an add-on to statins and supplemental eicosapentaenoic acid (EPA) on sdLDL-cholesterol and absorption of EPA in patients with coronary artery disease.

Methods: The study population consisted of 10 male patients who were concurrently receiving statins and EPA 1800 mg/day. Serum lipids and PUFAs, including EPA and arachidonic acid, were measured in blood samples collected before ezetimibe (baseline), 4 weeks after starting 10-mg/day ezetimibe, and 4 weeks after discontinuing ezetimibe.

Results: Ezetimibe significantly decreased sdLDL-cholesterol levels after 4 weeks of treatment (baseline, 35 ± 13 mg/dl; treatment, 27 ± 9 mg/dl), but the levels returned to baseline after discontinuation of ezetimibe (37 ± 13 mg/dl). The concentration of EPA did not significantly change during the study.

Conclusion: Ezetimibe shows great promise as an add-on therapy to statins to reduce sdLDL-cholesterol–related residual risk of cardiovascular disease without affecting absorption of supplemental EPA in patients with coronary artery disease.

Key Points: Ezetimibe may be useful for secondary prevention of cardiovascular disease in patients with atherogenic dyslipidemia without affecting absorption affecting supplemental eicosapentaenoic acid, which is potentially preventive agent for cardiovascular disease.

Introduction

Decreasing low-density lipoprotein (LDL)-cholesterol levels is the primary goal in the management of dyslipidemia in patients at high risk of cardiovascular disease [1-3]. Despite the use of statins which enable the achievement of targeted LDL-cholesterol levels, a substantial number of coronary events still occur [4, 5], which may result, in part, from elevated levels of triglycerides and triglyceride-rich lipoprotein remnants, and low levels of high-density lipoprotein (HDL)-cholesterol, which are often accompanied by high levels of small, dense LDL (sdLDL)-cholesterol. This combination is referred to as atherogenic dyslipidemia [6], which is highly prevalent in patients with diabetes mellitus or metabolic syndrome. In the Effect of Potentially Modifiable Risk Factors Associated With Myocardial Infarction in 52 Countries (INTERHEART) study, the risk associated with atherogenic dyslipidemia was shown to be independent to LDL-cholesterol levels [7]. To reduce the risk of coronary artery disease (CAD) further, secondary therapies to increase HDL-cholesterol, decrease triglycerides and triglyceride-rich lipoprotein remnants, and lower sdLDL-cholesterol levels may be recommended for patients who had achieved LDL-cholesterol levels below the currently recommended targets.

Ezetimibe, a cholesterol-absorption inhibitor, is used as an alternative to statins and as an add-on therapy for the reduction of LDL-cholesterol levels [8-10]. Ezetimibe decreases sdLDL-cholesterol levels when used in combination with statins[11, 12], whereas eicosapentaenoic acid (EPA), an *n*-3 polyunsaturated fatty acid (PUFA), has been shown to lower sdLDL-cholesterol levels, alone or in combination with statins [13, 14]. Thus, combined treatment with a statin, ezetimibe, and EPA may have the potential to lower triglycerides and sdLDL-cholesterol levels in patients with atherogenic dyslipidemia. However, the effects of this triple therapy on sdLDL-cholesterol levels have not been fully elucidated. In addition, a previous

animal study showed that ezetimibe significantly reduced absorption of dietary saturated fatty acids, but only a small effect was observed for the unsaturated fatty acids [15]. In humans, the effect of ezetimibe on absorption of EPA remains unclear.

The aim of this study was to evaluate if ezetimibe, as an add-on therapy to statin and EPA therapy, could lower sdLDL-cholesterol levels in patients with CAD, and if add-on ezetimibe affects the absorption of supplemental EPA.

Methods

Participants and design.

This study was approved by the Ethics Committee of Okayama University Hospital and Tamashima Central Hospital, and written informed consent was obtained from all participants before beginning the protocol. This study was conducted according to the principles expressed in the Declaration of Helsinki. The study is registered at UMIN Clinical Trials Registry (UMIN000012589). Schema of the study design is shown in **Fig.** 1.

This prospective study consisted of 10 outpatients with CAD who visited Tamashima Central Hospital (Okayama, Japan) regularly from May 2013 to November 2013. All enrolled patients had been receiving a statin and EPA (1800 mg/day) for dyslipidemia and secondary prevention of CAD for >3 months. Patients were excluded from the study if they had experienced acute coronary syndromes, stroke, or heart failure; had undergone major surgery <3 months before enrollment; or had variant angina, concomitant inflammatory diseases, or malignant tumors. Hypertension was defined as a seated blood pressure ≥140/90 mmHg or current use of antihypertensive agents. Diabetes was defined as fasting blood glucose ≥126 mg/dl and hemoglobinA1c ≥6.5%, or as requiring antidiabetic agents. Dyslipidemia was diagnosed according to the 2012 Japan Atherosclerotic Society guidelines or as concurrent treatment with a cholesterol-lowering agents[16]. Pre-specified primary outcome measure was the difference in sdLDL-cholesterol after ezetimibe treatment, and secondary outcome measure was the difference in *n*-3 PUFAs after ezetimibe treatment. Blood samples were collected prior to ezetimibe administration (baseline), 4 weeks after starting ezetimibe, and 4 weeks after discontinuation of ezetimibe.

Blood Examination.

Venous blood samples were obtained from the patients when they visited the outpatient clinic after overnight fasting for 8–12 hours. Serum lipid (total cholesterol, HDL-cholesterol, and triglyceride were measured using an autoanalyzer and routine methods at the central laboratory of Tamashima Central Hospital. LDL-cholesterol levels were calculated using Friedewald's equation[17, 18]. The serum levels of fatty acids and sdLDL-cholesterol in fasting blood samples were analyzed at SRL Company Ltd. (Tokyo, Japan). In brief, for measuring fatty acids, the lipid fraction was extracted from serum into chloroform/methanol using Folch's procedure, and then fatty acids (tricosanoic acid, C23:0, as the internal standard) were methylated with boron trifluoride and methanol. The methylated fatty acids were then analyzed using a capillary gas chromatograph (GC-2010; Shimadzu, Kyoto, Japan) and a BPX70 capillary column (0.25 mm internal diameter × 30 m; SGE International Ltd., Melbourne, Australia). We measured *n*-3 PUFA including EPA and docosahexaenoic acid (DHA) and *n*-6 PUFA including arachidonic acid (AA), dihomo-γ-linolenic acid (DGLA). SdLDL-cholesterol was measured using commercially available assay kit (sdLDL-EX; Denka Seiken Co.,Tokyo, Japan) as previously described[19].

Statistical Analysis.

Continuous variables are expressed as the mean ± standard deviation. Categorical variables are expressed as the number and percentage. Differences among the three time points were compared by repeated measures analysis of variance (ANOVA) with covariates including age, gender, current smoking, hypertension, and diabetes mellitus, and then followed by the Bonferroni post-hoc test. A value of $p < 0.05$ was considered significant. Calculations were performed using SPSS 17.0 for Windows (SPSS Inc., Chicago, IL, USA).

Results

The baseline characteristics of the study participants are shown in **Table 1**. The 10 participants were all men (mean age, 70 years). The statins used were pravastatin, two patients (10 mg/day); atorvastatin, six patients (10 mg/day); and rosuvastatin, two patients (2.5 mg/day). Patients with diabetes mellitus accounted for 40%. All patients maintained their body mass index during this study (at baseline, 26.1 ± 4.9 kg/m^2; at 4 weeks after treatment; 26.2 ± 5.6 kg/m^2, and at 4 weeks after discontinuation, 26.2 ± 5.2 kg/m^2).

Changes in serum lipids and PUFAs in the 10 patients are shown in **Table 2** and **Fig 2**. Ezetimibe treatment for 4 weeks significantly decreased the concentrations of total cholesterol, LDL-cholesterol, and sdLDL-cholesterol (**Fig 2A**), which returned to near baseline levels at 4 weeks after discontinuation of ezetimibe. The concentration of triglyceride tended to reduce for 4 weeks of ezetimibe treatment and returned to near baseline levels at 4 weeks after discontinuation of ezetimibe. Ezetimibe, however, did not significantly affect HDL-cholesterol, EPA (**Fig. 2B**), DHA, DGLA, or AA levels during the study period (**Table 2**). Consequently, ezetimibe did not affect the ratio of EPA to AA. HemoglobinA1c, serum creatine, and creatine kinase were also did not change during this study (**Table 2**). There were no significant change in systolic blood pressure and diastolic blood pressure during this study period (systolic pressure/diastolic pressure at baseline, 125 ± 13 / 67 ± 8 mmHg; at 4 weeks after treatment; 126 ± 14 /70 ± 8 mmHg, and at 4 weeks after discontinuation 124 ±13 /71 ± 9 mmHg). No clinical or laboratory adverse events or discontinuation occurred during the study period.

Discussion

This study demonstrated that ezetimibe in addition to statins and EPA significantly decreased sdLDL-cholesterol levels, but did not affect the absorption of supplemental EPA in patients with CAD. For secondary prevention of CAD, ezetimibe in addition to statins and EPA may be useful for controlling residual risks.

Although the patients in this study achieved considerable reduction in LDL-cholesterol levels (<100 mg/dl) with a statin and supplemental EPA, we found that ezetimibe successfully reduced LDL-cholesterol levels even further. The fact that sdLDL-cholesterol levels returned to baseline values after discontinuation of ezetimibe clearly shows the effect of ezetimibe on lowering sdLDL-cholesterol levels. This finding was consistent with previous studies that ezetimibe alone or in combination with a statin lowered sdLDL-cholesterol levels in patients with in patients with diabetes and glucose intolerance. [11, 12] In contrast, a recent study showed that treatment with ezetimibe alone or in combination with a statin increases sdLDL-cholesterol in healthy individuals [20]. This data suggested that ezetimibe was associated with the development of a pro-atherogenic LDL subfraction profile in subjects with a normal metabolic condition. The effect of ezetimibe on sdLDL-cholesterol is still argued, because the lack of clinical evidence of ezetimibe in cardiovascular events despite its significant LDL-cholesterol lowering effect; however, larger study is warranted to evaluate the effect of ezetimibe on sdLDL-cholesterol in patients with hypercholesterolemia or hypertriglyceridemia. Furthermore, our study demonstrates that ezetimibe decreases hypertriglyceridemia in patients receiving a statin and supplemental EPA, which is consistent with our previous findings that co-administration of ezetimibe and a statin reduce triglyceride levels in CAD patients[8]. Thus, ezetimibe in combination with a statin and EPA may be useful for reduction of residual risks, especially for secondary prevention of CAD.

We also demonstrated that ezetimibe did not affect serum *n*-3 PUFA concentrations in patients receiving supplemental EPA. The mammalian cholesterol-transport protein Niemann-Pick C1-like 1 is located on the surface of enterocytes[21]. In mice, ezetimibe treatment or lack of Niemann-Pick C1-like 1 significantly reduces absorption of dietary saturated fatty acids, particularly stearate and palmitate, but has only a small effect on absorption of the unsaturated fatty acids oleate and linoleate[15]. These results are consistent with the effects of ezetimibe on the PUFAs that we measured. Conversely, Kurisu et al. recently reported that strong statins reduce serum *n*-3 PUFA concentrations in proportion to the attendant decrease in LDL-cholesterol levels[22]. This difference on absorption of *n*-3 PUFAs by statins and ezetimibe is clinically interesting. These results suggest that ezetimibe may be a preferred therapy for patients with atherogenic dyslipidemia, however further investigation is needed to determine the optimal combination of therapies that will lower sdLDL-cholesterol levels in the absence of undesired side effects such as a decrease in *n*-3 PUFA levels.

Previous studies suggested potential beneficial effects of *n*-3 PUFAs on cardiovascular disease [23-25], while recent cardiovascular outcome studies on *n*-3 PUFA therapy have been disappointing [26-28]. One possible reason of this discrepancy was the dose of n-3 PUFA. Harris et al. reported that greater fatty acid composition in red blood cell membrane was associated with the greater cardioprotection [29]; however, the 2013 AHA/ACC Cardiovascular Risk Reduction Guideline does not recommend strongly the supplemental use of *n*-3 PUFA [30]. Further studies are needed to assess *n*-3 PUFA therapies in the context of clinical care using larger patient populations and larger doses, while a lot of epidemiologic studies showed that low *n*-3 PUFA level is a risk of CAD. [31-33] Thus, Inhibition of absorption of *n*-3 PUFA is not favorable; therefore our finding that ezetimibe did not affect EPA level may be informative.

Limitations to our study include: 1) this was an open-label add-on study. Evaluation at 4 weeks after discontinuation of ezetimibe and careful statistical analyses may have compensated for this limitation; however, there is no doubt that a larger study, preferably with a double-blind crossover, multi-center design, will be required to confirm our findings. 2) We measured the concentrations of EPA, DHA, DGLA, and AA, but did not evaluate their proportions relative to total free fatty acids. 3) This study included only a small number of patients with CAD on a particular combination treatment regimen, making it difficult to generalize the results to other populations.

Conclusions

Ezetimibe in addition to statins and EPA significantly decreased sdLDL-cholesterol, but did not affect serum EPA concentrations in patients with CAD. Ezetimibe may be a promising agent as an add-on therapy to statins and EPA to reduce residual risks in patients with CAD.

Conflict of interest: None

Acknowledgements: None

References

1. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). Lancet. 1994 Nov 19;344(8934):1383-9.

2. Long-term effectiveness and safety of pravastatin in 9014 patients with coronary heart disease and average cholesterol concentrations: the LIPID trial follow-up. Lancet. 2002 Apr 20;359(9315):1379-87.

3. Sacks FM, Pfeffer MA, Moye LA, Rouleau JL, Rutherford JD, Cole TG, et al. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. Cholesterol and Recurrent Events Trial investigators. N Engl J Med. 1996 Oct 3;335(14):1001-9.

4. Alagona P, Jr. Beyond LDL cholesterol: the role of elevated triglycerides and low HDL cholesterol in residual CVD risk remaining after statin therapy. Am J Manag Care. 2009 Mar;15(3 Suppl):S65-73.

5. Nakamura T, Obata JE, Hirano M, Kitta Y, Fujioka D, Saito Y, et al. Predictive value of remnant lipoprotein for cardiovascular events in patients with coronary artery disease after achievement of LDL-cholesterol goals. Atherosclerosis. 2011 Sep;218(1):163-7.

6. Austin MA, King MC, Vranizan KM, Krauss RM. Atherogenic lipoprotein phenotype. A proposed genetic marker for coronary heart disease risk. Circulation. 1990 Aug;82(2):495-506.

7. Yusuf S, Hawken S, Ounpuu S, Dans T, Avezum A, Lanas F, et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. Lancet. 2004 Sep 11-17;364(9438):937-52.

8. Yunoki K, Nakamura K, Miyoshi T, Enko K, Kubo M, Murakami M, et al. Impact of hypertriglyceridemia on endothelial dysfunction during statin +/- ezetimibe therapy in patients

with coronary heart disease. Am J Cardiol. 2011 Aug 1;108(3):333-9.

9. Nakamura T, Hirano M, Kitta Y, Fujioka D, Saito Y, Kawabata K, et al. A comparison of the efficacy of combined ezetimibe and statin therapy with doubling of statin dose in patients with remnant lipoproteinemia on previous statin therapy. J Cardiol. 2012 Jul;60(1):12-7.

10. Uemura Y, Watarai M, Ishii H, Koyasu M, Takemoto K, Yoshikawa D, et al. Atorvastatin 10 mg plus ezetimibe 10mg compared with atorvastatin 20 mg: impact on the lipid profile in Japanese patients with abnormal glucose tolerance and coronary artery disease. J Cardiol. 2012 Jan;59(1):50-6.

11. Tsunoda T, Nozue T, Yamada M, Mizuguchi I, Sasaki M, Michishita I. Effects of ezetimibe on atherogenic lipoproteins and glucose metabolism in patients with diabetes and glucose intolerance. Diabetes Res Clin Pract. 2013 Apr;100(1):46-52.

12. Winkler K, Jacob S, Muller-Schewe T, Hoffmann MM, Konrad T. Ezetimibe alone and in combination lowers the concentration of small, dense low-density lipoproteins in type 2 diabetes mellitus. Atherosclerosis. 2012 Jan;220(1):189-93.

13. Nordoy A, Hansen JB, Brox J, Svensson B. Effects of atorvastatin and omega-3 fatty acids on LDL subfractions and postprandial hyperlipemia in patients with combined hyperlipemia. Nutr Metab Cardiovasc Dis. 2001 Feb;11(1):7-16.

14. Satoh N, Shimatsu A, Kotani K, Sakane N, Yamada K, Suganami T, et al. Purified eicosapentaenoic acid reduces small dense LDL, remnant lipoprotein particles, and C-reactive protein in metabolic syndrome. Diabetes Care. 2007 Jan;30(1):144-6.

15. Labonte ED, Camarota LM, Rojas JC, Jandacek RJ, Gilham DE, Davies JP, et al. Reduced absorption of saturated fatty acids and resistance to diet-induced obesity and diabetes by ezetimibe-treated and Npc1l1-/- mice. Am J Physiol Gastrointest Liver Physiol. 2008

Oct;295(4):G776-83.

16. Teramoto T, Sasaki J, Ishibashi S, Birou S, Daida H, Dohi S, et al. Executive summary of the Japan Atherosclerosis Society (JAS) guidelines for the diagnosis and prevention of atherosclerotic cardiovascular diseases in Japan -2012 version. J Atheroscler Thromb. 2013;20(6):517-23.

17. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clin Chem. 1972 Jun;18(6):499-502.

18. Schectman G, Patsches M, Sasse EA. Variability in cholesterol measurements: comparison of calculated and direct LDL cholesterol determinations. Clin Chem. 1996 May;42(5):732-7.

19. Ito Y, Fujimura M, Ohta M, Hirano T. Development of a homogeneous assay for measurement of small dense LDL cholesterol. Clin Chem. 2011 Jan;57(1):57-65.

20. Berneis K, Rizzo M, Berthold HK, Spinas GA, Krone W, Gouni-Berthold I. Ezetimibe alone or in combination with simvastatin increases small dense low-density lipoproteins in healthy men: a randomized trial. Eur Heart J. 2010 Jul;31(13):1633-9.

21. Altmann SW, Davis HR, Jr., Zhu LJ, Yao X, Hoos LM, Tetzloff G, et al. Niemann-Pick C1 Like 1 protein is critical for intestinal cholesterol absorption. Science. 2004 Feb 20;303(5661):1201-4.

22. Kurisu S, Ishibashi K, Kato Y, Mitsuba N, Dohi Y, Nishioka K, et al. Effects of lipid-lowering therapy with strong statin on serum polyunsaturated fatty acid levels in patients with coronary artery disease. Heart Vessels. 2013 Jan;28(1):34-8.

23. Dietary supplementation with n-3 polyunsaturated fatty acids and vitamin E after

myocardial infarction: results of the GISSI-Prevenzione trial. Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico. Lancet. 1999 Aug 7;354(9177):447-55.

24. Tavazzi L, Maggioni AP, Marchioli R, Barlera S, Franzosi MG, Latini R, et al. Effect of n-3 polyunsaturated fatty acids in patients with chronic heart failure (the GISSI-HF trial): a randomised, double-blind, placebo-controlled trial. Lancet. 2008 Oct 4;372(9645):1223-30.

25. Yokoyama M, Origasa H, Matsuzaki M, Matsuzawa Y, Saito Y, Ishikawa Y, et al. Effects of eicosapentaenoic acid on major coronary events in hypercholesterolaemic patients (JELIS): a randomised open-label, blinded endpoint analysis. Lancet. 2007 Mar 31;369(9567):1090-8.

26. Bosch J, Gerstein HC, Dagenais GR, Diaz R, Dyal L, Jung H, et al. n-3 fatty acids and cardiovascular outcomes in patients with dysglycemia. N Engl J Med. 2012 Jul 26;367(4):309-18.

27. Kromhout D, Giltay EJ, Geleijnse JM. n-3 fatty acids and cardiovascular events after myocardial infarction. N Engl J Med. 2010 Nov 18;363(21):2015-26.

28. Rauch B, Schiele R, Schneider S, Diller F, Victor N, Gohlke H, et al. OMEGA, a randomized, placebo-controlled trial to test the effect of highly purified omega-3 fatty acids on top of modern guideline-adjusted therapy after myocardial infarction. Circulation. 2010 Nov 23;122(21):2152-9.

29. Harris WS, Von Schacky C. The Omega-3 Index: a new risk factor for death from coronary heart disease? Prev Med. 2004 Jul;39(1):212-20.

30. Eckel RH, Jakicic JM, Ard JD, Hubbard VS, de Jesus JM, Lee IM, et al. 2013 AHA/ACC Guideline on Lifestyle Management to Reduce Cardiovascular Risk: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2013 Nov 12.

31. Albert CM, Hennekens CH, O'Donnell CJ, Ajani UA, Carey VJ, Willett WC, et al. Fish consumption and risk of sudden cardiac death. JAMA. 1998 Jan 7;279(1):23-8.

32. Kromhout D, Bosschieter EB, de Lezenne Coulander C. The inverse relation between fish consumption and 20-year mortality from coronary heart disease. N Engl J Med. 1985 May 9;312(19):1205-9.

33. Lemaitre RN, King IB, Mozaffarian D, Kuller LH, Tracy RP, Siscovick DS. n-3 Polyunsaturated fatty acids, fatal ischemic heart disease, and nonfatal myocardial infarction in older adults: the Cardiovascular Health Study. Am J Clin Nutr. 2003 Feb;77(2):319-25.

Table 1. Participant characteristics.

Number of patients	10
Age (years)	70 ± 7
Body mass index (kg/m^2)	26.1 ± 4.9
Abdominal circumference (cm)	94.5 ± 13.5
Hypertension	9 (90%)
Diabetes Mellitus	4 (40%)
Previous coronary heart disease	7 (70%)
Fasting blood glucose (mg/dl)	122 ± 20
Systolic blood pressure (mmHg)	125 ± 13
Diastolic blood pressure (mmHg)	67 ± 8
Currently smoking	5 (50%)
Concomitant medication	
Eicosapentaenoic acid	10 (100%)
Statins	
Pravastatin	2 (20%)
Atorvastatin	6 (60%)
Rosuvastatin	2 (20%)
Antihypertensive agents	
ACEI/ARBs	9 (90%)
Calcium channel blockers	4 (40%)
β-blockers	7 (70%)
Antidiabetic agents	

Insulin	2 (20%)
Thiazolidinedione	2 (20%)
DPP4 inhibitor	3 (30%)
α-Glucosidase inhibitor	1 (10%)

ACEI; angiotensin-converting enzyme inhibitor, ARB; angiotensin II type 1 receptor blocker, DPP4; dipeptidyl peptidase 4.

Table 2. Serum lipid, polyunsaturated fatty acid levels, and other parameters before ezetimibe, 4 weeks after starting ezetimibe, and 4 weeks after discontinuation of ezetimibe.

	Baseline	4 weeks after ezetimibe start	4 weeks after ezetimibe end
Total Cholesterol	155 ± 17	136 ± 15*	165 ± 26†
LDL-cholesterol (mg/dl)	81 ± 21	63 ± 15*	86 ± 29†
HDL-cholesterol (mg/dl)	48 ± 14	50 ± 16	52 ± 16
Triglyceride (mg/dl)	212 ± 49	168 ± 60	222 ± 99
sdLDL-cholesterol (mg/dl)	35 ± 13	27 ± 9*	37 ± 13†
EPA (μg/ml)	213 ± 58	208 ± 83	218 ± 81
DHA (μg/ml)	170 ± 84	163 ± 89	165 ± 90
AA (μg/ml)	173 ± 27	186 ± 56	175 ± 24
DGLA (μg/ml)	32 ± 9	32 ± 6	33 ± 6
EPA/AA	1.25 ± 0.33	1.15 ± 0.38	1.25 ± 0.43
HemoglobinA1c (%)	6.5 ± 0.8	6.5 ± 0.7	6.5 ± 0.7
Serum creatinine (mg/dl)	0.96 ± 0.15	0.91 ± 0.20	0.87 ± 0.20
Creatine kinase (U/l)	95 ± 52	97 ± 90	104 ± 76

LDL, low-density lipoprotein; HDL, high-density lipoprotein; sd, small dense; AA, arachidonic acid; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid; DGLA, dihomo-γ-linolenic acid.

*, $p < 0.05$ versus baseline; †, $p < 0.05$ versus 4 weeks after treatment with ezetimibe. Differences among the three time points were compared by repeated measures analysis of variance (ANOVA) with covariates including age, current smoking, hypertension, and diabetes mellitus, and then followed by the Bonferroni post-hoc test.

Legends for Figures

Figure 1. Schema of the study design. EPA; eicosapentaenoic acid.

Figure 2. Effects of ezetimibe on sdLDL- cholesterol andeicosapentaenoic acid in all patients. SdLDL- cholesterol levels (A) and eicosapentaenoic acid levels (B) at baseline, 4 weeks after start of ezetimibe and 4 weeks after discontinuation of ezetimibe. Open circle indicates the mean value. *p<0.05 versus 4 weeks after ezetimibe start. sdLDL, small dense low-density lipoprotein. Differences among the three time points were compared by repeated measures analysis of variance (ANOVA) with covariates including age, current smoking, hypertension, and diabetes mellitus, and then followed by the Bonferroni post-hoc test.