Original Research

Comparison of the Efficacy and Safety of Atorvastatin 40 mg/ω-3 Fatty Acids 4 g Fixed-dose Combination and Atorvastatin 40 mg Monotherapy in Hypertriglyceridemic Patients who Poorly Respond to Atorvastatin 40 mg Monotherapy: An 8-week, Multicenter, Randomized, Double-blind Phase III Study

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ABSTRACT

Purpose: Residual cardiovascular risk in patients with hypertriglyceridemia, despite optimal low-density lipoprotein cholesterol levels being achieved with intensive statin treatment, is a global health issue. The purpose of this study was to investigate the efficacy and tolerability of treatment with a combination of high-dose atorvastatin/Ω-3 fatty acid

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compared to atorvastatin + placebo in patients with hypertriglyceridemia who did not respond to statin treatment.

Methods: In this multicenter, randomized, double-blind, placebo-controlled study, patients who had residual hypertriglyceridemia after a 4-week run-in period of atorvastatin treatment were randomly assigned to receive UI-018 (fixed-dose combination atorvastatin/Ω-3 fatty acid 40 mg/4 g) or atorvastatin 40 mg + placebo (control). The primary efficacy end points were the percentage change from baseline in non–high density lipoprotein cholesterol (non–HDL-C) level at the end of treatment and the adverse events recorded during treatment. A secondary end point was the percentage change from baseline in triglyceride level.

Findings: After 8 weeks of treatment, the percentage changes from baseline in non–HDL-C (–4.4% vs +0.6%; $p = 0.02$) and triglycerides (–18.5% vs +0.9%; $p < 0.01$) were significantly greater in the UI-018 group ($n = 101$) than in the control group ($n = 99$). These changes were present in subgroups of advanced age (≥65 years), status (body mass index ≥25 kg/m^2), or without diabetes. The prevalences of adverse events did not differ between the 2 treatment groups.

Implications: In patients with residual hypertriglyceridemia despite receiving statin treatment, a combination of high-dose atorvastatin/Ω-3 fatty acid was associated with a greater reduction of triglyceride and non–HDL-C compared with atorvastatin + placebo, without significant adverse events. (*Clin Ther.* 2021;43:1419–1430.)

Key words: Ω-3 fatty acid, atorvastatin, combination treatment, hypertriglyceridemia, non–HDL-C.

INTRODUCTION

Current guidelines on dyslipidemia recommend statin treatment to prevent or manage atherosclerotic cardiovascular diseases, and low density lipoprotein cholesterol (LDL-C) is a primary target of treatment.[1–3] A recent change in the LDL-C target goal requires the use of high-intensity statin treatment or combination therapy. These recommendations were based on widespread evidence regarding statins with respect to the greatest reduction in the risk for cardiovascular events with the best margin of safety. However, there was a residual risk for cardiovascular events despite a reduction in LDL-C of >50% with the use of high-intensity statin or ezetimibe combination treatments or new targeted therapy agents. Previous studies suggested that hypertriglyceridemia is an independent risk factor for atherosclerotic cardiovascular disease.[4,5] However, triglycerides (TG) and non-high density lipoprotein cholesterol (non–HDL-C) are recommended as secondary targets for preventing atherosclerotic cardiovascular disease in patients with mixed dyslipidemia who achieve the LDL-C target. Even with more potent statin treatment, some patients experience hypertriglyceridemia and require additional agents to control their TG level. Niacin, fibrate and Ω-3 fatty acid products are treatment modalities well-known for controlling serum TG levels. Ω-3 Fatty acid products, including eicosapentaenoic acid (EPA), have been shown to bring about a 25% to 30% reduction in serum TG level.[6] Additionally, recent clinical trials and meta-analyses have demonstrated that EPA and statin combination treatment significantly reduced the prevalence of major adverse cardiovascular events (MACE).[7–9] Some studies have indicated the benefit and tolerability of combination treatment with a statin and Ω-3 fatty acid,[10–13] but few data are available regarding the efficacy and tolerability of the proved dose of EPA and a high-intensity statin in patients with residual hypertriglyceridemia after statin treatment. This Phase III study was designed to assess the effects and tolerability of atorvastatin 40 mg/d in combination with Ω-3 fatty acid 4 g/d in patients with hypertriglyceridemia despite having received treatment with atorvastatin 40 mg/d, compared to atorvastatin 40 mg/d + placebo.

PATIENTS AND METHODS

Study Design

This Phase III 8-week, multicenter, randomized, double-blind, parallel-group study was conducted at 22 sites in Korea between November 2017 and December 2019. The clinical trial protocol and method of obtaining informed consents were approved by the Korean Food and Drug Administration and the local ethics review boards of each hospital. The study was conducted in accordance with the ethics principles of the current Declaration of Helsinki, and patients signed

informed-consent documents prior to any relevant laboratory tests being conducted.

Subjects with mixed dyslipidemia who were in the category of very high risk for cardiovascular disease were screened at the first visit in accordance with the guideline.[14] After >4 weeks of therapeutic lifestyle changes, patients who fulfilled the following criteria were eligible: (1) patients with coronary artery disease (history of myocardial infarction, unstable angina, coronary intervention or including myocardial ischemia with clinical significance) or equivalent risk with respect to coronary artery disease (diabetes, other atherosclerotic disease or 10-year risk for coronary artery disease >20% with 2 or more risk factors); (2) patients whose fasting TG level was between 200 and 500 mg/dL (except those who had received a TG-modifying agent in the preceding 4 weeks), or those with a LDL-C level of >110 mg/dL (except those who received a statin in the preceding 4 weeks); and (3) patients whose LDL-C level needed to be reduced by >45%.

These patients underwent a 4-week run-in period of open-label treatment with atorvastatin 40 mg/d. After the run-in period, the levels of LDL-C and TGs were measured repeatedly for the second screening. The participants who were taking atorvastatin for over 4 weeks and met the primary screening criteria with regard to cholesterol profile could visit for the second screening without a run-in period. To be eligible for the second screening, participants met the following criteria: (1) residual hypertriglyceridemia with a fasting TG level between 200 and 500 mg/dL; (2) a well-controlled LDL-C level according to the guideline[14]; (3) those who had a medication adherence rate of ≥80% during the run-in period. The exclusion criteria included: (1) a history of unstable angina, acute myocardial infarction, coronary artery revascularization (including coronary artery bypass surgery), transient ischemic attack, or cerebrovascular disease 12 weeks before screening; (2) a history of malignant tumor in the preceding 5 years, except for complete resolution of basal cell or squamous cell carcinoma; (3) drug or alcohol abuse; (4) malabsorption syndrome with a history of gastrointestinal surgery or gastrointestinal dysfunction; (5) uncontrolled hypertension (defined as systolic blood pressure [BP] of ≥180 mm Hg and/or diastolic BP of ≥110 mm Hg); (6) uncontrolled diabetes (defined as hemoglobin A_{1c} of ≥9%); (7) uncontrolled hypothyroidism (defined as thyroid stimulating hormone levels ≥1.5-fold the upper limit of normal [× ULN]); (8) alanine aminotransferase and/or aspartate aminotransferase level of ≥2 × ULN; (9) serum creatinine level of ≥2 × ULN and/or creatinine clearance of <30 mL/min; (10) serum creatine kinase level of ≥2 × ULN; (11) a history of symptoms of unexplained myalgia or a diagnosis of myalgia or rhabdomyolysis; (12) pancreatitis prior to screening or at screening; (13) significant comorbid medical illness in cardiovascular, hepatobiliary, neuropsychiatric, endocrine systems that posed difficulties in continuing the clinical trial and interpreting test results; (14) allergy or hypersensitivity to the study medications; (15) pregnancy or breast-feeding at screening; (16) possible or planned pregnancy during the clinical trial; (17) inclusion in another clinical trial 1 month prior to screening; and (18) other conditions that were not appropriate for the clinical trial.

Finally, eligible subjects were randomly assigned in a 1:1 ratio to 1 of 2 groups (UI-018 or atorvastatin group) for 8 weeks. A fixed-dose combination of Ω-3 fatty acid 1 g + atorvastatin calcium 10 mg was formulated for this study. Individuals in the UI-018 group were prescribed 4 capsules of preformed fixed-dose combination agent and 1 tablet of placebo of atorvastatin. The atorvastatin group received 4 capsules of placebo of UI-018 and 1 tablet of atorvastatin calcium 40 mg (Figure 1).

Study End Points

The primary efficacy end points were the percentage changes in non–HDL-C levels from baseline to week 8 of treatment. Secondary end points included percentage change in other lipid and lipoprotein parameters, such as TG, total cholesterol (TC), LDL-C, HDL-C, very–low-density lipoprotein cholesterol (VLDL-C), apolipoprotein (apo) A-I, and apo B, LDL-C/HDL-C ratio, TC/HDL-C ratio, non–HDL-C/HDL-C ratio, and apo B/apo A-I ratio after 4 and 8 weeks of treatment. Lipids, including LDL-C, were measured by the laboratories of each hospital using standard procedures.

Tolerability assessments were performed at each visit and included adverse events, vital signs, physical examination, electrocardiography, and clinical laboratory tests, including serum chemical analysis and urinalysis. Adverse events were defined as "occurred," "worsened," or "became serious" during the study period, and included all unintended consequences

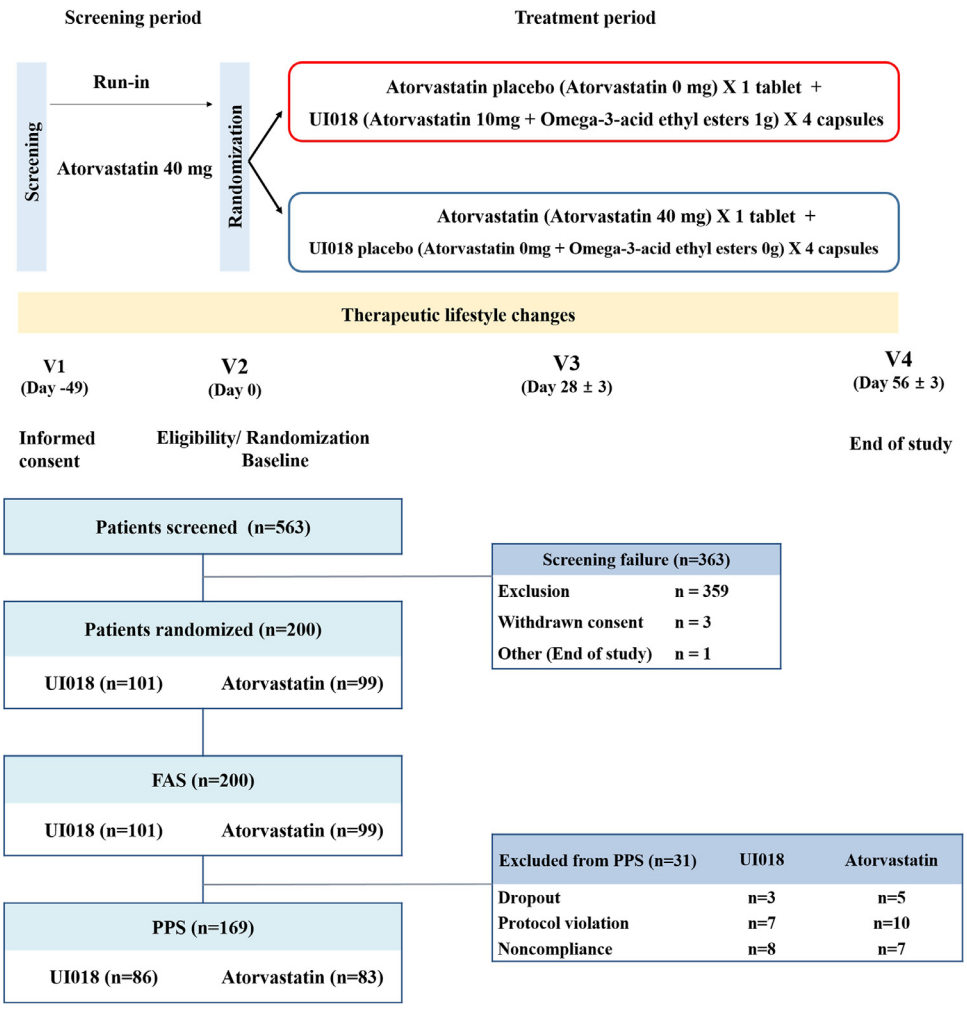

Figure 1. Study protocol. After a 4-week run-in period with atorvastatin 40 mg, eligible patients were randomly assigned to receive treatment with a fixed-dose combination of atorvastatin/Ω-3 fatty acid 40 mg/4 g (UI-018) or atorvastatin 40 mg + placebo for 8 weeks. FAS = full analysis set; PPS = per-protocol set.

stemming from the individual receiving treatment, regardless of the causality. Adverse events were categorized as "definitely related," "probably related," "possibly related," "probably not related," "definitely not related," and "with unknown relationship to the study drug."

Statistical Analysis

From previous studies,[10] a sample size of 160 patients (80 patients in each treatment group) was required to provide a statistical power of 80% and a probability of a type I error of 0.05 using a 2-sided test. At least 200 patients were registered on the basis of the assumption of a 20% dropout rate.

The analyses were performed using SAS version 9.3 (SAS Institute, Cary, North Carolina). Efficacy end points were compared between the UI-018 and atorvastatin groups with the use of ANCOVA with baseline values as covariates. Normality assumptions were investigated with the Anderson-Darling test on the residuals. If the normality assumption was rejected ($p < 0.01$), values were analyzed using ranked ANCOVA. A p value of <0.05 was considered statistically significant. Continuous variables were presented as mean (SD) if normally distributed, or as median

(25th–75th percentile) if not normally distributed. The comparison of data from the two groups was performed by using the 2-sample t test or Wilcoxon rank sum test according to normal distribution. Categorical variables, presented as frequencies and percentages, were compared using the χ^2 test or Fisher exact test when appropriate. The percentage changes in TG and other cholesterol values between the treatment groups were compared using ANCOVA. Efficacy analyses involved a full analysis set population, which comprised those who received at least 1 dose of the study drug and provided at least 1 post-randomization blood sample. Tolerability analyses were performed on data from the safety set population, defined as those who received at least 1 dose of double-blind study drug and underwent at least 1 tolerability assessment after randomization.

RESULTS

Patients' Characteristics

As shown in Figure 1, a total of 563 patients were screened for eligibility, with 200 patients (35.5%) undergoing randomization (101 to the UI-018 group and 99 to the atorvastatin group). The entire randomized population was included in the full analysis set because all patients underwent non–HDL-C evaluation at baseline and after 8-week study drug treatment. From the randomized population, 18 patients in the UI-018 group and 22 patients in the atorvastatin group were excluded from the full analysis set population because they did not meet the eligibility criteria or because they failed to comply with the clinical guidelines. Finally, data from 159 patients (79.5%) (79 in the UI-018 group and 80 in the atorvastatin group) were included in the evaluation of the efficacy end points for the per-protocol analysis.

Table I shows the demographic and clinical characteristics at baseline for all randomized patients. Most parameters were similar between the 2 groups except for sex, weight, and body mass index (BMI); patients in the UI-018 group had a greater mean body weight and BMI.

Efficacy End Points

Table II summarizes the lipid and lipoprotein parameters at baseline and differences in responses to the allocation of the 2 treatments. The percentage change from baseline in non–HDL-C after 8 weeks was significantly greater in the UI-018 group compared to the atorvastatin monotherapy group (-4.4% vs +0.6%, respectively; $p = 0.02$). There was also a greater reduction in TG level in the UI-018 group than in the atorvastatin group (–18.5% vs +0.9%; $p < 0.01$). Additionally, the UI-018 group showed significant reductions in TC, VLDL-C, the ratio of TC/HDL-C, and the ratio of non–HDL-C/HDL-C compared to those in the atorvastatin group (Figure 2). But the percentage changes in LDL-C, HDL-C, apo A1, and apo B were not statistically different between the 2 groups. Meanwhile, per-protocol analysis showed significant reductions in non–HDL-C, TG, and VLDL-C in the UI-018 group. The percentages of patients who achieved non–HDL-C target goals were not significantly different between the 2 groups after 4 weeks of treatment, but the difference after 8 weeks of treatment was significant (87.1% vs 72.7%; $p = 0.01$).

In subgroup analysis, both non–HDL-C (Figure 3) and TG (Figure 4) levels showed greater reductions in the UI-018 group than in the atorvastatin group after 8 weeks of treatment among patients who were elderly (aged ≥65 years), (BMI ≥25 kg/m^2), or nondiabetic.

Tolerability

During the study period, there was no significant difference in the overall prevalences of adverse events (20.8% in the UI-018 group vs 15.2% in the atorvastatin group; hazard ratio = 1.08 [95% CI, –0.05 to 0.16]; $P = 0.36$). One case of a serious adverse event occurred in each group: uremia in the UI-018 group and acute myocardial infarction in the atorvastatin group. As shown in Table III, the most frequent adverse event was gastrointestinal dysfunction (5.9% in the UI-018 group vs 5.0% in the atorvastatin group). None of these were considered related to the study treatment. There were no significant increases in laboratory test values (serum alanine aminotransferase, aspartate aminotransferase, creatinine, creatinine kinase levels) in either group.

DISCUSSION

This study showed that a combination treatment of Ω-3 fatty acid and atorvastatin achieved a greater reduction in TG, non–HDL-C, and other lipid parameters than atorvastatin monotherapy did in patients with residual hypertriglyceridemia. These effects were more potent in patients who were elderly, or nondiabetic. Additionally,

Table I. Demographic and clinical characteristics at baseline.

Characteristic	UI-018 (n = 101)	Atorvastatin (n = 99)	p
Age, mean (SD), y	59	60	0.47
Male, no. (%)	89 (88)	73 (74)	<0.01
Body mass index, mean (SD), kg/m^2	26.8 (2.6)	25.5 (2.9)	<0.01
Risk factors			
Hypertension, no. (%)	81 (80)	74 (75)	0.36
Diabetes mellitus, no. (%)	44 (44)	49 (49)	0.43
Current smoker, no. (%)	39 (39)	31 (31)	0.28
Any use of alcohol, no. (%)	64 (63)	60 (61)	0.47
10-Year risk score for CHD, mean (SD), %	11.8 (7.1)	10.6 (7.5)	0.11
History of statin use, no. (%)	100 (99)	97 (98)	0.62
History of TG-lowering agents, no. (%)	12 (14)	8 (9)	0.31

CHD = coronary heart disease; TG = triglyceride.

Table II. Mean (SD) lipid and lipoprotein levels before and after 8-week treatment.

Blood Component	UI-018 (n = 101)			Atorvastatin (n = 99)			P*
	Baseline, mg/dL	Week 8, mg/dL	Percentage Change	Baseline, mg/dL	Week 8, mg/dL	Percentage Change	
Non–HDL-C	107.7 (23.8)	100.1 (28.9)	–4.4 (31.4)	113.4 (23.9)	112.6 (33.8)	+0.6 (25.9)	0.02†
TG	294.2 (79.0)	231.2 (114.8)	–18.5 (44.4)	297.1 (85.3)	290.3 (149.3)	+0.9 (51.8)	<0.01†
TC	148.7 (26.8)	141.6 (30.2)	–3.7 (17.6)	154.4 (25.5)	153.2 (34.0)	0.0 (19.0)	0.04†
LDL-C	73.9 (23.3)	72.6 (25.4)	+1.2 (27.5)	79.7 (23.1)	77.4 (26.9)	–0.7 (27.3)	0.86†
HDL-C	41.0 (9.1)	41.5 (9.6)	+2.0 (14.5)	41.1 (8.3)	40.6 (7.6)	+0.3 (16.5)	0.42‡
VLDL-C	33.8 (10.3)	27.5 (15.3)	–14.1 (57.6)	33.6 (14.0)	35.1 (21.8)	+15.8 (95.5)	<0.01†
Apo A1	138.2 (23.2)	132.5 (22.5)	–3.5 (11.7)	138.0 (21.2)	133.2 (20.3)	–2.8 (12.4)	0.67‡
Apo B	82.1 (18.4)	80.3 (20.9)	+0.3 (26.5)	88.7 (18.7)	85.7 (22.5)	–1.9 (22.2)	0.84†

Apo = apolipoprotein; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; TC = total cholesterol; TG = triglyceride; VLDL-C = very–low-density lipoprotein cholesterol.

*For between-treatment difference in percentage changes.

†The analysis was performed using ranked ANCOVA.

‡The analysis was performed using ANCOVA.

there were no significant adverse effects considered as related to treatment with 4 g/d of Ω-3 fatty acid and 40 mg/d of atorvastatin in these Korean patients.

LDL-C is a key target in the prevention and reduction of MACE. The 2013 American College of Cardiology/American Heart Association guideline recommended the 4 statin benefit groups (established atherosclerotic cardiovascular disease; LDL-C ≥ 190 mg/dL with age ≥21 years; Age 40-75 with diabetes, LDL-C 70-189 mg/dL; Age 40-75 without atherosclerotic cardiovascular disease or diabetes, 10-year risk ≥ 7.5%) and initiated statin treatment regardless

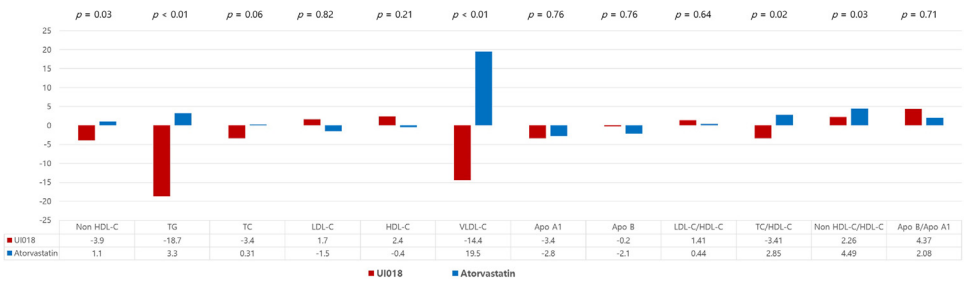

Figure 2. Percentage changes in lipid parameters from baseline after 8 weeks of treatment. Apo = apolipoprotein A1; HDL-C = high density lipoprotein cholesterol; LDL-C = low density lipoprotein cholesterol; TC = total cholesterol; TG = triglycerides; VLDL-C = very–low-density lipoprotein cholesterol.

of LDL-C level.[1] Following the 2018 ACC/AHA guideline, a target value of LDL-C <70mg/dL or >50% reduction was proposed in very–high-risk groups.[2] The 2019 guideline from the European Society of Cardiology and European Atherosclerosis Society recommended that LDL-C be reduced to as low a level as possible, at least in patients at very high risk.[3] The current notion regarding LDL-C can be summarized as, "Lower is better, earlier is better, and combination is better." However, patients with LDL-C <70 mg/dL undergoing statin therapy continue to experience cardiovascular events. Even though numerous studies have demonstrated the association of high TG and low HDL-C with regard to atherosclerosis or cardiovascular events, there have been very few clinical trials seeking to reduce adverse cardiovascular events by targeting TG or HDL-C level.[15–18] Because there is little evidence regarding the additional benefit of reducing cardiovascular events, current guidelines do not recommend TG-lowering treatment or HDL-C–elevating agents as primary prevention methods.

The Dyslipidemia Fact Sheet in Korea 2018 revealed that the prevalence of hypertriglyceridemia was 17.5% in the general population,[19] and the Korean acute myocardial infarction registry also revealed that there was a high prevalence of hypertriglyceridemia (about 20%) when it is defined as a TG level of >150 mg/dL in the fasting state.[20] Even though the prevalence of hypertriglyceridemia in Asia is relatively higher than in Western populations,[21] hypertriglyceridemia is still a significant residual cardiovascular risk in both Asian and Western populations. Hokanson and Austin[22] found that cardiovascular risk is increased by ~30% in men and 75% in women with respect to a 1-mmol/L increase in TG level. They also found that hypertriglyceridemia is an important risk factor for cardiovascular disease for both men and women in the general population, independent of HDL-C. This is linked to the circumstance in which an increase in TG levels directly or indirectly affects obesity, metabolic syndrome, and type 2 diabetes.[23–25]

Elevated TG level is a modifiable risk factor to reduce the global burden beyond LDL-C. Ω-3 Fatty acid was suggested as a promising agent to reduce cardiovascular risks by reducing TG and elevating HDL-C levels. However, it did not show consistent results regarding cardiovascular benefits in subsequent Alpha-Ω, Ω, ORIGIN and FORWARD trials.[15,16,26,27] Recent clinical trials have reported that the risk for cardiovascular disease can be significantly reduced by controlling TG with highly purified EPA. The large-scale randomized, open-labelled clinical Japan EPA Lipid Intervention Study was designed to investigate the effects of EPA administration on cardiovascular risk in hypertriglyceridemic patients[7] and reported that combination treatment with Ω-3 fatty acids (EPA 1.8 g/d) and a statin could significantly reduce the prevalence of MACE by 19% compared to controls. Another clinical trial showed the beneficial effect of combination treatment with a statin and Ω-3 fatty acids.[10–13] In 254 patients with hypertriglyceridemia, patients were randomly assigned to receive combination treatment with simvastatin 40 mg + Ω-3 fatty acids 4 g or simvastatin 40 mg monotherapy.[10] With combination treatment, TG level was significantly reduced, by a mean of 29.5%, compared to that with statin monotherapy.[10] Additionally, other lipid parameters such as TC, VLDL-

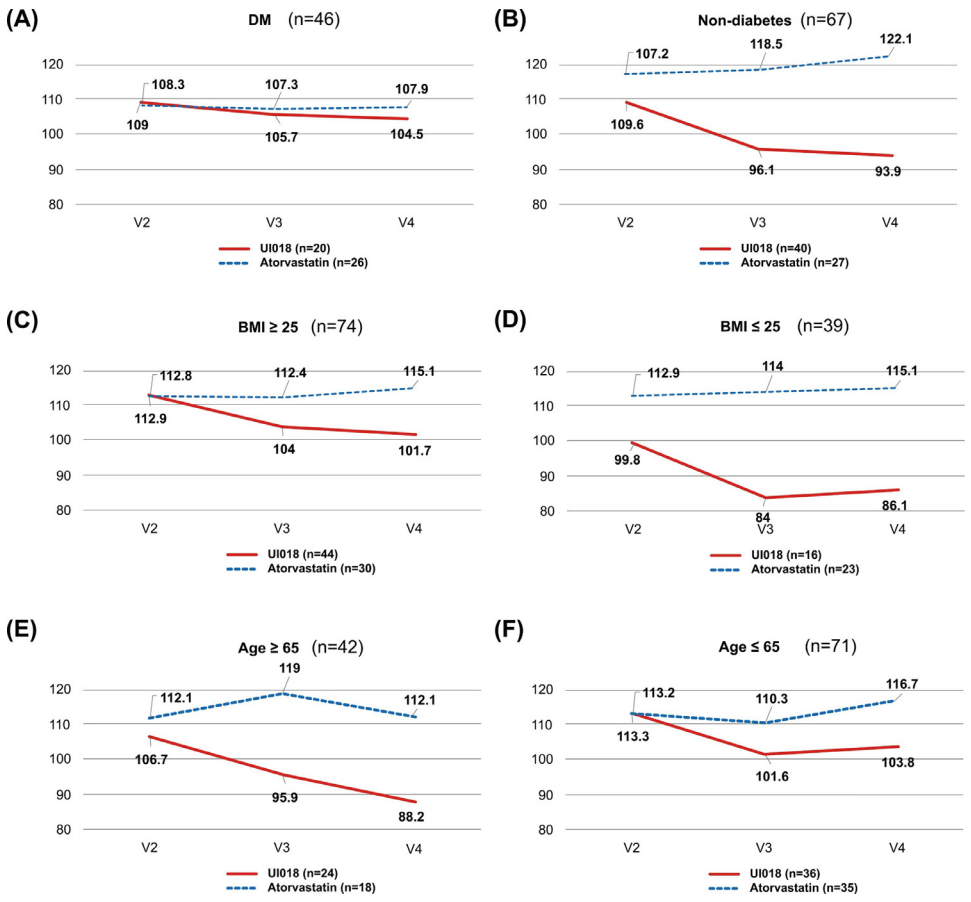

Figure 3. Subgroup analysis of serial changes in non–high-density lipoprotein cholesterol (non–HDL-C). BMI = body mass index; DM = diabetes mellitus.

C, and HDL-C were decreased with as much statistical significance as our result.[10] Compared to the previous studies,[10–13] we evaluated atorvastatin 40 mg + Ω-3 fatty acids 4 g combination treatment, in which the statin dose was classified as high intensity. Although the ROMANTIC (Rosuvastatin-Omacor in Residual Hypertriglyceridemia) study[12] demonstrated that a subgroup with a lower BMI benefited further with regard to lipid profile, the present study showed in the contrary. It is unclear whether this is from the different class effect of atorvastatin, or from other factors. The mean BMI was significantly higher in the UI-018 group despite appropriate randomization. The reason would be the difference in the composition of men and women. More men were enrolled in the UI-018 group, so the mean BMI would have been higher. Even though this study showed that the lipid-modifying effects of combination treatment were profound in patients with a high BMI compared to monotherapy, we could not rule out the possibility of randomization bias, and the importance of weight reduction and lifestyle changes in TG reduction should be kept in mind. The US Food and Drug Administration has approved diet supplementation with Ω-3 fatty acid with in patients in whom TG exceeds 496 mg/dL based on these results. Bhatt et al[8] also published results from clinical trials demonstrating the benefits of higher-dose EPA + a statin for cardiovascular risk reduction. A recent meta-analysis demonstrated that when EPA was combined with statin therapy, the prevalence of MACEs was significantly reduced, mainly driven by a significant reduction in myocardial infarction.[9]

The mechanisms by which Ω-3 fatty acids prevent coronary artery disease are thought to be related to

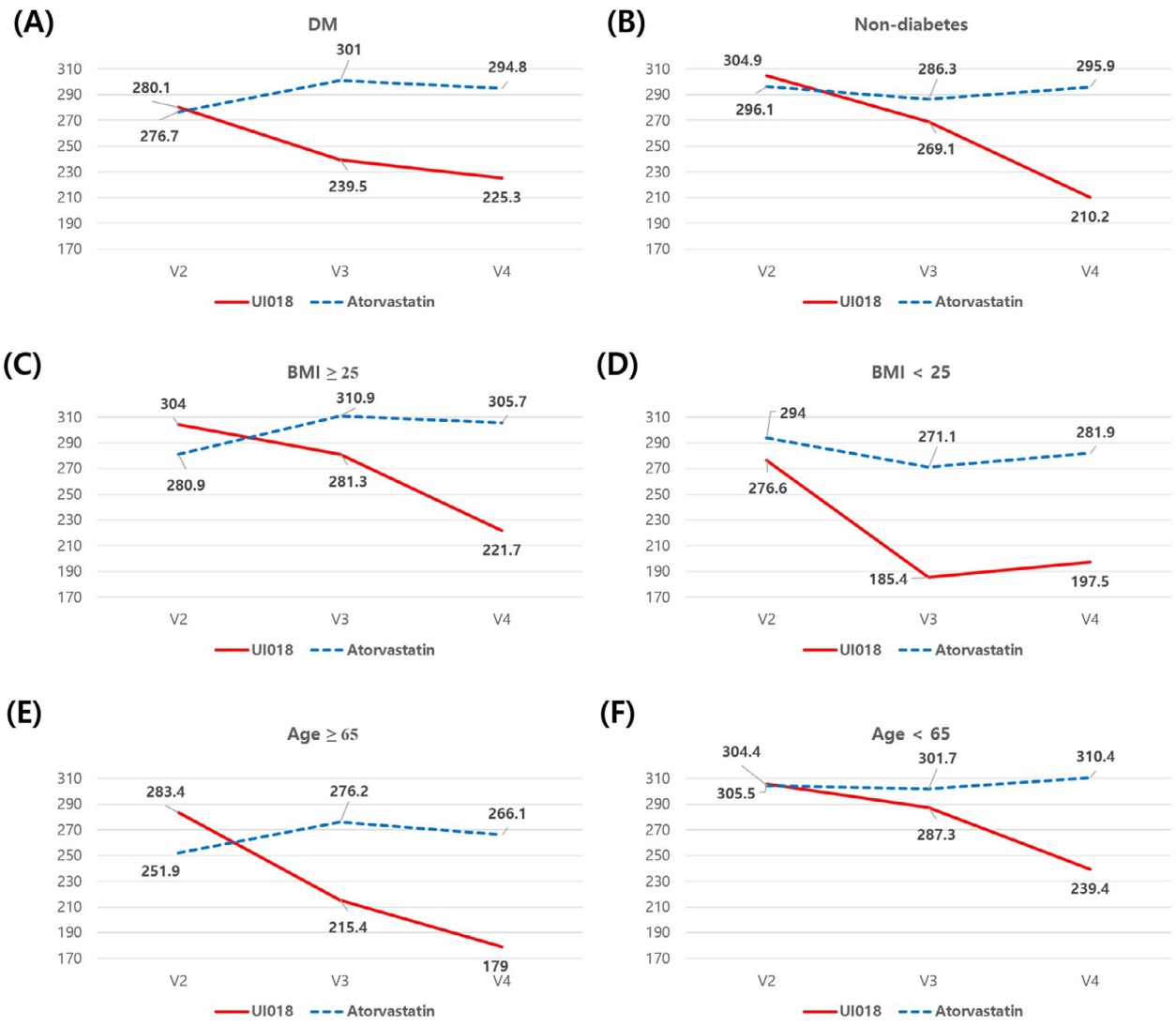

Figure 4. Subgroup analysis of serial changes in triglycerides (TG). BMI = body mass index; DM = diabetes mellitus.

the inhibition of vascular calcium, reduction of platelet reactivity, and slowing the progression of atherosclerosis.[7,28–31] The EVAPORATE (Effect of Icosapent Ethyl on Progression of Coronary Atherosclerosis in Patients with Elevated Triglycerides on Statin Therapy) study[31] demonstrated a significant improvement in plaque progression, suggesting a mechanism of cardiovascular benefit in the REDUCE-IT (Effect of Icosapent Ethyl on Progression of Coronary Atherosclerosis in Patients With Elevated Triglycerides on Statin Therapy) trial.[8] Additionally, a large-scale meta-analysis evaluated the BP-lowering effects of Ω-3 fatty acids.[32] The diastolic BP was decreased after the administration of >2 g of EPA + docosahexaenoic acid, and the systolic BP was also decreased by daily treatment of 1~2 g of EPA + docosahexaenoic acid. This suggests that Ω-3 fatty acid, EPA, and docosahexaenoic acid, can act as antioxidants, which are associated with inflammation and atherosclerosis. From this perspective, Ω-3 fatty acid can be used to prevent coronary artery disease and improve lipid profiles in patients with residual hypertriglyceridemia after statin treatment. This study was conducted among patients who respond poorly to high-intensity statin treatment.

Table III. Treatment-emergent adverse events. Data are given as number (%) of patients.

Event	UI-018 (n = 101)	Atorvastatin (n = 99)
Gastrointestinal disorders		
Dental hyperesthesia	2 (4)	2 (2)
Diarrhea	1 (1)	1 (1)
Nausea	1 (1)	1 (1)
Constipation	1 (1)	0
Dyspepsia	1 (1)	0
Toothache	0	1 (1)
Skin and subcutaneous tissue disorders		
Pruritus	2 (2)	1 (1)
Allergic dermatitis	0	1 (1)
Erythema	0	1 (1)
Infections and infestations		
Upper respiratory tract infection	1 (1)	2 (2)
Herpes zoster	1 (1)	0
Nervous system disorders		
Headache	1 (1)	0
Dizziness	0	1 (1)
General disorders		
Facial edema	1 (1)	0
Orbital edema	0	1
Other		
Hematuria	1 (1)	0
HbA_{1c} ≥9% on OHA treatment	0	1
Myalgia	0	1

Hb = hemoglobin; OHA = oral hypoglycemic agent.

As current guidelines consistently recommend high-intensity statin treatment (atorvastatin 40 mg or 80 mg, rosuvastatin 20 or 40 mg), this present study has significance in that it showed significantly improved lipid parameters without any concerns regarding tolerability.

Limitations with respect to this study include the following. First, this study demonstrated the short-term effects of Ω-3 fatty acid and atorvastatin combination treatment in a small sample size. Additionally, the study does not prove that there is a reduction of cardiovascular events by improving lipid profiles. The study population was also exclusively middle-aged Koreans, which means the results cannot be extrapolated or generalized to the whole population. However, this study also confirmed the lipid-lowering effects and tolerability of high doses Ω-3 fatty acid and statin combination treatment. Further large-scale, multinational randomized studies are needed to show the cardiovascular benefits with tolerability. Finally, this study did not show the effects according to dose differences of Ω-3 fatty acid and statin combination treatment. But proven EPA dose by recent trials would be equivalent to 4 g of Ω-3 fatty acid and guidelines recommend the high intensity statin. This study could contribute to answering questions about the effects and tolerability of a proven dose.

CONCLUSION

In conclusion, Ω-3 fatty acid (4 g/d) and atorvastatin (40 mg/d) combination treatment decreases TG, non–HDL-C, and other lipid parameters compared to atorvastatin monotherapy in patients with residual hyper-

triglyceridemia despite having received statin treatment for 8 weeks. These beneficial effects were more prominent in patients that were elderly, or non-diabetic.

AUTHOR CONTRIBUTIONS

Substantial contributions to the conception and design, acquisition of data, or analysis and interpretation of data were made by J.S. Woo, S.J. Hong, D.H. Cha, K.S. Kim, M.H. Kim, J.W. Lee, M.H. Jeong, J.O. Jeong, J.H. Lee, D.S. Jeon, E.J. Cho, S.K. Kim, J. Kwan, C.G. Park, H.Y. Lee, T.J. Hong, J.H. Shin, H.J. Youn, D.W. Jeon, W.J. Chung, J.C. Jeong, and C.J. Kim. Drafting the article or revising it critically for important intellectual content was performed by J.S. Woo, S.J. Hong, J.W. Lee, E.J. Cho, H.J. Youn, and C.J. Kim. Final approval of the version to be published was provided by J.S. Woo, S.J. Hong, D.H. Cha, K.S. Kim, M.H. Kim, J.W. Lee, M.H. Jeong, J.O. Jeong, J.H. Lee, D.S. Jeon, E.J. Cho, S.K. Kim, J. Kwan, C.G. Park, H.Y. Lee, T.J. Hong, J.H. Shin, H.J. Youn, D.W. Jeon, W.J. Chung, J.C. Jeong, and C.J. Kim.

DISCLOSURES

The authors have indicated that they have no conflicts of interest with regard to the content of this article.

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REFERENCES

1. Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the management of blood cholesterol: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2019;73:e285–e350.
2. Arnett DK, Blumenthal RS, Albert MA, et al. 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation*. 2019;140:e563–e595.
3. Mach F, Baigent C, Catapano AL, et al. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. *Eur Heart J*. 2020;41:111–188.
4. Johansen CT, Hegele RA. Using mendelian randomization to determine causative factors in cardiovascular disease. *J Intern Med*. 2013;273:44–47.
5. Jorgensen AB, Frikke-Schmidt R, West AS, et al. Genetically elevated non-fasting triglycerides and calculated remnant cholesterol as causal risk factors for myocardial infarction. *Eur Heart J*. 2013;34:1826–1833.
6. Harris WS. Ω-3 fatty acids and serum lipoproteins: human studies. *Am J Clin Nutr*. 1997;65(5 Suppl):1645S–1654S.
7. Yokoyama M, Origasa H, Matsuzaki M, et al. Effects of eicosapentaenoic acid on major coronary events in hypercholesterolaemic patients (JELIS): a randomised open-label, blinded endpoint analysis. *Lancet*. 2007;369(9567):1090–1098.
8. Bhatt DL, Steg PG, Miller M, et al. Cardiovascular risk reduction with icosapent ethyl for hypertriglyceridemia. *N Engl J Med*. 2019;380:11–22.
9. Doshi R, Kumar A, Thakkar S, et al. Meta-analysis comparing combined use of eicosapentaenoic acid and statin to statin alone. *Am J Cardiol*. 2020;125:198–204.
10. Davidson MH, Stein EA, Bays HE, et al. Efficacy and tolerability of adding prescription omega-3 fatty acids 4 g/d to simvastatin 40 mg/d in hypertriglyceridemic patients: an 8-week, randomized, double-blind, placebo-controlled study. *Clin Ther*. 2007;29:1354–1367.
11. Maki KC, Lubin BC, Reeves MS, Dicklin MR, Harris WS. Prescription omega-3 acid ethyl esters plus simvastatin 20 and 80 mg: effects in mixed dyslipidemia. *J Clin Lipidol*. 2009;3:33–38.
12. Kim CH, Han KA, Yu J, et al. Efficacy and safety of adding omega-3 fatty acids in statin-treated patients with residual hypertriglyceridemia: ROMANTIC (Rosuvastatin-OMAcor iN residual hyperTrIglyCeridemia), a randomized, double-blind, and placebo-controlled trial. *Clin Ther*. 2018;40:83–94.
13. Jun JE, Jeong IK, Yu JM, et al. Efficacy and safety of Omega-3 fatty acids in patients treated with statins for residual hypertriglyceridemia: a randomized, double-blind, placebo-controlled clinical trial. *Diabet Metab J*. 2020;44:78–90.
14. Catapano AL, Graham I, De Backer G, et al. 2016 ESC/EAS guidelines for the management of dyslipidaemias. *Eur Heart J*. 2016;37:2999–3058.
15. Kromhout D, Giltay EJ, Geleijnse JM, et al. Alpha Omega Trial G. Ω-3 fatty acids and cardiovascular events after myocardial infarction. *N Engl J Med*. 2010;363:2015–2026.
16. Rauch B, Schiele R, Schneider S, 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;122:2152–2159.

17. Schwartz GG, Olsson AG, Abt M, et al. Effects of dalcetrapib in patients with a recent acute coronary syndrome. *N Engl J Med*. 2012;367:2089–2099.
18. Bowman L, Hopewell JC, et al. HPS3/TIMI55–REVEAL Collaborative Group. Effects of anacetrapib in patients with atherosclerotic vascular disease. *N Engl J Med*. 2017;377:1217–1227.
19. Rhee EJ. Prevalence and current management of cardiovascular risk factors in Korean adults based on fact sheets. *Endocrinol Metab (Seoul)*. 2020;35:85–94.
20. Kim KH, Kim CH, Jeong MH, et al. Differential benefit of statin in secondary prevention of acute myocardial infarction according to the level of triglyceride and high density lipoprotein cholesterol. *Korean Circ J*. 2016;46:324–334.
21. Frank AT, Zhao B, Jose PO, Azar KM, Fortmann SP, Palaniappan LP. Racial/ethnic differences in dyslipidemia patterns. *Circulation*. 2014;129:570–579.
22. Hokanson JE, Austin MA. Plasma triglyceride level is a risk factor for cardiovascular disease independent of high-density lipoprotein cholesterol level: a meta-analysis of population-based prospective studies. *J Cardiovasc Risk*. 1996;3:213–219.
23. Budoff M. Triglycerides and triglyceride-rich lipoproteins in the causal pathway of cardiovascular disease. *Am J Cardiol*. 2016;118:138–145.
24. Sandesara PB, Virani SS, Fazio S, Shapiro MD. The forgotten lipids: triglycerides, remnant cholesterol, and atherosclerotic cardiovascular disease risk. *Endocr Rev*. 2019;40:537–557.
25. Henriksbo BD, Tamrakar AK, Xu J, et al. Statins promote interleukin-1β-dependent adipocyte insulin resistance through lower prenylation, not cholesterol. *Diabetes*. 2019;68:1441–1448.
26. Gerstein HC, Bosch J, et al. ORIGIN Trial Investigators. Basal insulin and cardiovascular and other outcomes in dysglycemia. *N Engl J Med*. 2012;367:319–328.
27. Macchia A, Grancelli H, Varini S, et al. Omega-3 fatty acids for the prevention of recurrent symptomatic atrial fibrillation: results of the FORWARD (Randomized Trial to Assess Efficacy of PUFA for the Maintenance of Sinus Rhythm in Persistent Atrial Fibrillation) trial. *J Am Coll Cardiol*. 2013;61:463–468.
28. Calder PC, Yaqoob P. Marine omega-3 fatty acids and coronary heart disease. *Curr Opin Cardiol*. 2012;27:412–419.
29. Iso H, Kobayashi M, Ishihara J, et al. Intake of fish and Ω-3 fatty acids and risk of coronary heart disease among Japanese: the Japan Public Health Center-Based (JPHC) Study Cohort I. *Circulation*. 2006;113:195–202.
30. De Caterina R. Ω-3 fatty acids in cardiovascular disease. *N Engl J Med*. 2011;364:2439–2450.
31. Budoff MJ, Bhatt DL, Kinninger A, et al. Effect of icosapent ethyl on progression of coronary atherosclerosis in patients with elevated triglycerides on statin therapy: final results of the EVAPORATE trial. *Eur Heart J*. 2020 Aug 29:[Epub ahead of print].
32. Miller PE, Van Elswyk M, Alexander DD. Long-chain omega-3 fatty acids eicosapentaenoic acid and docosahexaenoic acid and blood pressure: a meta-analysis of randomized controlled trials. *Am J Hypertens*. 2014;27:885–896.

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