



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

Chee Hae Kim, MD¹; Kyung Ah Han, MD, PhD²; Jaemyung Yu, MD, PhD³; Sang Hak Lee, MD, PhD⁴; Hui Kyung Jeon, MD, PhD⁵; Sang Hyun Kim, MD, PhD⁶; Seok Yeon Kim, MD, PhD⁷; Ki Hoon Han, MD, PhD⁸; Kyungheon Won, MD, PhD⁷; Dong-Bin Kim, MD, PhD⁹; Kwang-Jae Lee, MD, PhD¹⁰; Kyungwan Min, MD, PhD²; Dong Won Byun, MD, PhD¹¹; Sang-Wook Lim, MD, PhD¹²; Chul Woo Ahn, MD, PhD¹³; SeongHwan Kim, MD, PhD¹⁴; Young Joon Hong, MD, PhD¹⁵; Jidong Sung, MD, PhD¹⁶; Seung-Ho Hur, MD, PhD¹⁷; Soon Jun Hong, MD, PhD¹⁸; Hong-Seok Lim, MD, PhD¹⁹; le Byung Park, MD, PhD²⁰; In Joo Kim, MD, PhD²¹; Hyoungwoo Lee, MD, PhD²²; and Hyo-Soo Kim, MD, PhD¹

¹Department of Internal Medicine, Seoul National University Hospital, Cardiovascular Centre, Seoul, Korea; ²Diabetes Center, Eulji University, Seoul Eulji hospital, Seoul, Korea; ³Kangnam Sacred Heart Hospital, Seoul, Korea; ⁴Cardiology Division, Yonsei University College of Medicine, Severance Cardiovascular Hospital, Seoul, Korea; ⁵Department of Internal Medicine, Division of Cardiology, The Catholic University of Korea, Seoul, Korea; ⁶Department of Cardiology, Boramae Medical Center, Seoul National University College of Medicine, Seoul, Korea; ⁷Department of Internal Medicine, Seoul Medical Center, Seoul, Korea; ⁸Departments of Cardiology, Ischemic Heart Disease Center, Asan Medical Center Heart Institute, Seoul, Korea; ⁹Department of Cardiology, Catholic University of Korea College of Medicine, Seoul, Korea; ¹⁰Department of Endocrinology, Daedong Hospital, Seoul, Korea; ¹¹Endocrinology and Metabolism, Soonchunhyang University Hospital, Seoul, Korea; ¹²Department of Cardiology, Bundang Cha General Hospital, Seoul, Korea; ¹³Department of Internal Medicine, Gangnam Severance Hospital, Seoul, Korea; ¹⁴Division of Cardiology, Department of Medicine, Korea University Ansan Hospital, Seoul, Korea; ¹⁵Heart Center of Chonnam National University Hospital, Chonnam National University, Seoul, Korea; ¹⁶Division of Cardiology, Cardiac and Vascular Center, Samsung Medical Center, Seoul, Korea; ¹⁷Department of Cardiology, Keimyung University Dongsan Hospital, Daegu, Korea; ¹⁸Korea University Medical Center, Korea University, Seoul, Korea; ¹⁹Department of Cardiology, Ajou University School of Medicine, Suwon, Korea; ²⁰Division of Endocrinology and Metabolism, Department of Internal Medicine, Gachon University Gil Medical Center, Incheon, Korea; ²¹Department of Internal Medicine, Pusan National University College of Medicine, Busan, Korea; and ²²Department of Internal Medicine, Yeungnam University College of Medicine, Daegu, Korea

ABSTRACT

Purpose: The purpose of this study was to examine the efficacy and safety of adding ω -3 fatty acids to rosuvastatin in patients with residual hypertriglyceridemia despite statin treatment.

Accepted for publication November 14, 2017.

<https://doi.org/10.1016/j.clinthera.2017.11.007>
0149-2918/\$ - see front matter

© 2018 The Authors. Published by Elsevier HS Journals, Inc. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Methods: This study was a multicenter, randomized, double-blind, placebo-controlled study. After a 4-week run-in period of rosuvastatin treatment, the patients who had residual hypertriglyceridemia were randomized to receive rosuvastatin 20 mg/d plus ω -3 fatty acids 4 g/d (ROSUMEGA group) or rosuvastatin 20 mg/d (rosuvastatin group) with a 1:1 ratio and were prescribed each medication for 8 weeks.

Findings: A total of 201 patients were analyzed (mean [SD] age, 58.1 [10.7] years; 62.7% male). After 8 weeks of treatment, the percentage change from baseline in triglycerides (TGs) and non-HDL-C was significantly greater in the ROSUMEGA group than in the rosuvastatin group (TGs: -26.3% vs -11.4%, $P < 0.001$; non-HDL-C: -10.7% vs -2.2%, $P = 0.001$). In the linear regression analysis, the lipid-lowering effect of ω -3 fatty acids was greater when baseline TG or non-HDL-C levels were high and body mass index was low. The incidence of adverse events was not significantly different between the 2 groups.

Implications: In patients with residual hypertriglyceridemia despite statin treatment, a combination of ω -3 fatty acids and rosuvastatin produced a greater reduction of TGs and non-HDL-C than rosuvastatin alone. Further study is needed to determine whether the advantages of this lipid profile of ω -3 fatty acids actually leads to the prevention of cardiovascular event. ClinicalTrials.gov identifier: NCT03026933. (*Clin Ther.* 2018;40:83–94) © 2018 The Authors. Published by Elsevier HS Journals, Inc.

Key words: combination, hypertriglyceridemia, non-HDL-C, ω -3 fatty acids, rosuvastatin, triglycerides.

INTRODUCTION

Control of blood cholesterol levels apparently reduces atherosclerotic cardiovascular disease.¹ The first recommended therapy for dyslipidemia is statins, which effectively prevents cardiovascular disease by lowering LDL-C levels. However, hypertriglyceridemia is also well known as an independent risk factor associated with cardiovascular events.^{2–4} Statins are not effective at lowering triglycerides (TGs), which partly explains the reason why cardiovascular events occur even with the use of statins. Therefore, in patients with mixed dyslipidemia, controlling TG levels

in addition to lowering LDL-C levels should be considered.

Treatment options to lower TG levels are fibrates, niacin, and ω -3 fatty acids.⁵ Among these, fibrates and niacin are associated with tolerability problems. Contrariwise, ω -3 fatty acids have proven its TG-lowering effect with good tolerability.⁶ However, there are mild LDL-C-increasing effects in ω -3 fatty acids.⁷ For appropriate combination therapy of statin and ω -3 fatty acids, further studies are needed.

Previous studies have found the efficacy of combining ω -3 fatty acids with several statins on controlling TG levels.^{8–10} However, the efficacy and tolerability of the combination of ω -3 fatty acids and rosuvastatin, which is the most potent statin currently used, have not yet been proven. This Phase III study aimed to examine the efficacy and safety of the combination of ω -3 fatty acids and rosuvastatin compared with rosuvastatin alone in patients with residual hypertriglyceridemia despite statin treatment.

METHODS

Study Design

The study was an 8-week, prospective, randomized, double-blind, parallel group, Phase III multicenter trial conducted in 33 centers in South Korea. The study period was from June 18, 2014, through March 31, 2016.

Patients with hypercholesterolemia at high risk for cardiovascular disease according to the National Cholesterol Education Program (NCEP): Adult Treatment Panel III (ATP III) were screened.¹¹ To be eligible in first screening, participants were required to meet the following criteria: (1) age from 19 to 80 years, (2) fasting TG level ≥ 300 mg/dL and LDL-C level ≥ 100 mg/dL and < 160 mg/dL for individuals who were not taking statins for 4 weeks, (3) TG level ≥ 200 mg/dL and < 500 mg/dL, and LDL-C level < 110 mg/dL for individuals who were taking statins for last 4 weeks, and (4) nonsmoking during the study period. Then eligible participants underwent a 4-week run-in period. During the run-in period, all participants received 20 mg/d of open-label rosuvastatin calcium and discontinued use of other lipid-lowering agents. After the run-in period, the levels of LDL-C and TGs were measured repeatedly. To be eligible in the second screening, participants were required to meet the

following criteria: (1) residual hypertriglyceridemia with fasting TG level ≥ 200 mg/dL and < 500 mg/dL, (2) well-controlled LDL-C level of < 110 mg/dL, (3) reduction of LDL-C levels during the run-in period comparing first screening if individuals were not taking statins before, and (4) those who had an adherence rate of $\geq 80\%$ for medication during the run-in period. The exclusion criteria included (1) history of unstable angina, acute myocardial infarction, coronary artery revascularization, including coronary artery bypass surgery, transient ischemic attack, or stroke 3 months before screening; (2) history of operation for aortic aneurysm within 6 months before screening; (3) symptom of unexplained myalgia or a diagnosis of myalgia or rhabdomyolysis at screening; (4) history of pancreatitis before screening; (5) uncontrolled hypertension; (6) serum creatinine level ≥ 2 times the upper limit of normal; (6) alanine aminotransferase and/or aspartate aminotransferase ≥ 3 times the upper limit of normal; (7) creatinine phosphokinase levels > 5 times the upper limit of normal; (8) genetic disorder, including galactose intolerance, Lapp lactase deficiency, or glucose-galactose malabsorption; (9) history of positive antibody HIV-1 or HIV test result; (10) history of malignant tumor within 5 years; and (11) the use of prohibited concomitant medications. The eligible patients were randomly assigned with a 1:1 ratio to 2 groups and prescribed ROSUMEGA or rosuvastatin for 8 weeks. Individuals in the ROSUMEGA group were prescribed 4 capsules of ω -3 fatty acids 1 g plus rosuvastatin calcium 5 mg and 1 tablet of placebo of rosuvastatin 20 mg/d. Each 1 g of ω -3 fatty acids contains 380 mg of docosahexaenoic acid and 460 mg of eicosapentaenoic acid. The rosuvastatin group received 4 capsules of placebo of ROSUMEGA and 1 tablet of rosuvastatin calcium 20 mg (Figure 1). On the basis of baseline data collected, an individual's 10-year risk of coronary heart disease was calculated according to NCEP ATP III.¹¹ The study protocol was approved by the institutional review board or ethics committee at each participating center, and all patients provided written informed consent.

Efficacy and Tolerability Assessments

The efficacy end points were the percentage change of lipid and lipoprotein levels, including TGs, non-HDL-C, total cholesterol, LDL-C, HDL-C, VLDL-C,

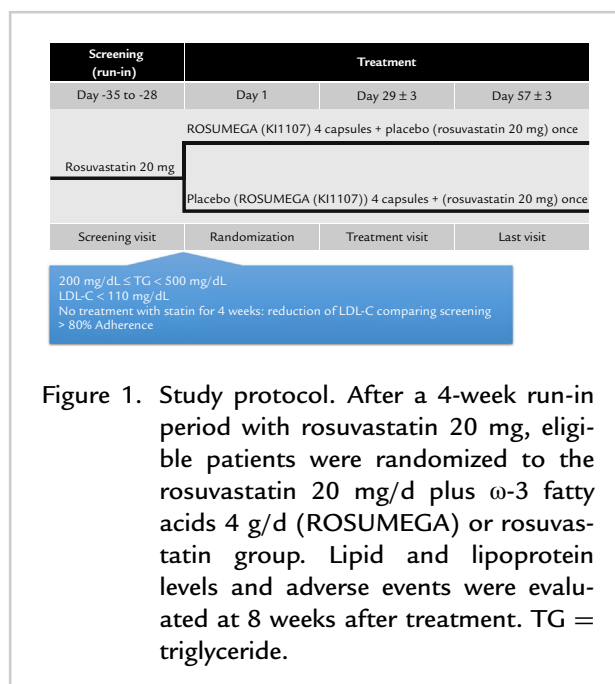


Figure 1. Study protocol. After a 4-week run-in period with rosuvastatin 20 mg, eligible patients were randomized to the rosuvastatin 20 mg/d plus ω -3 fatty acids 4 g/d (ROSUMEGA) or rosuvastatin group. Lipid and lipoprotein levels and adverse events were evaluated at 8 weeks after treatment. TG = triglyceride.

and apolipoprotein A1 and B (Apo A1 and Apo B) after 8 weeks from baseline.

Subgroup analyses were performed according to diabetes mellitus (DM), chronic kidney disease (CKD), age (≥ 65 vs < 65 years), and sex (male vs female) to determine whether the effects of ω -3 fatty acids differed in each subgroup. The study participants were classified into the DM group if they had a previous diagnosis of DM or who were currently taking oral hypoglycemic agents or insulins. The definition of CKD was a glomerular filtration rate < 60 mL/min per 1.73 m².¹²

Tolerability was assessed by monitoring of adverse events and performing physical examinations and laboratory tests, including serum chemical analyses and urinalysis. Adverse events included all unintended consequences of the individuals receiving treatment regardless of causality. Adverse drug reaction meant a harmful, unintended reaction, and the causal relationship with the treatment cannot be excluded. Adverse events were categorized as definitely related, probably related, possibly related, probably not related, and definitely not related to the study drug.

Statistical Analysis

Continuous variables were expressed as mean (SD) or mean (SE) as appropriate and compared with the

2-sample *t* test or Wilcoxon rank sum test according to normal distribution. Categorical variables were expressed as frequencies and percentages, and the χ^2 test was used for comparison. The differences of percentage changes in TG and other cholesterol values between the treatment groups were compared using the 2-sample *t* test if normally distributed and the Wilcoxon rank sum test if not normally distributed. To identify the clinical factors associated with the greater effect of ω -3 fatty acids in lowering TG and non-HDL-C levels, linear regression analyses were performed and the prediction model was obtained.

The efficacy analyses were performed using the full analysis set population and the safety analyses with the safety set population. Two-sided $P < 0.05$ was considered statistically significant. All analyses were performed using SAS, version 9.3 (SAS Institute, Cary, North Carolina) and SPSS, version 22.0 (IBM Co, Armonk, New York).

RESULTS

Baseline Characteristics

Of the 750 patients who were screened, 469 patients entered the run-in period, and 215 patients were randomly assigned to treatment groups. A total of 104 patients were assigned to the ROSUMEGA group and 111 patients to the rosuvastatin group. From the randomized population, 1 participant in each group were excluded from the safety set because they were not actually treated. Then the equal number of 6 patients in both groups was excluded from full analysis set population because of violation from eligibility criteria or inadequate laboratory test. Finally, 201 patients were analyzed for evaluating efficacy end points (Figure 2).

Baseline characteristics are summarized in Table I. Clinical characteristics were similar between the 2 groups except for age, with older subjects in the ROSUMEGA group than in the rosuvastatin group (mean [SD] age, 59.7 [10.8] vs 56.6 [10.5] years; $P = 0.040$). The mean (SD) 10-year risk score for coronary heart disease was 10.5% (6.9%) in the ROSUMEGA group and 8.8% (6.5%) in the rosuvastatin group ($P = 0.085$). There was no difference in the proportion of patients who previously used statins between the 2 groups (92.8% vs 95.2%, $P = 0.471$).

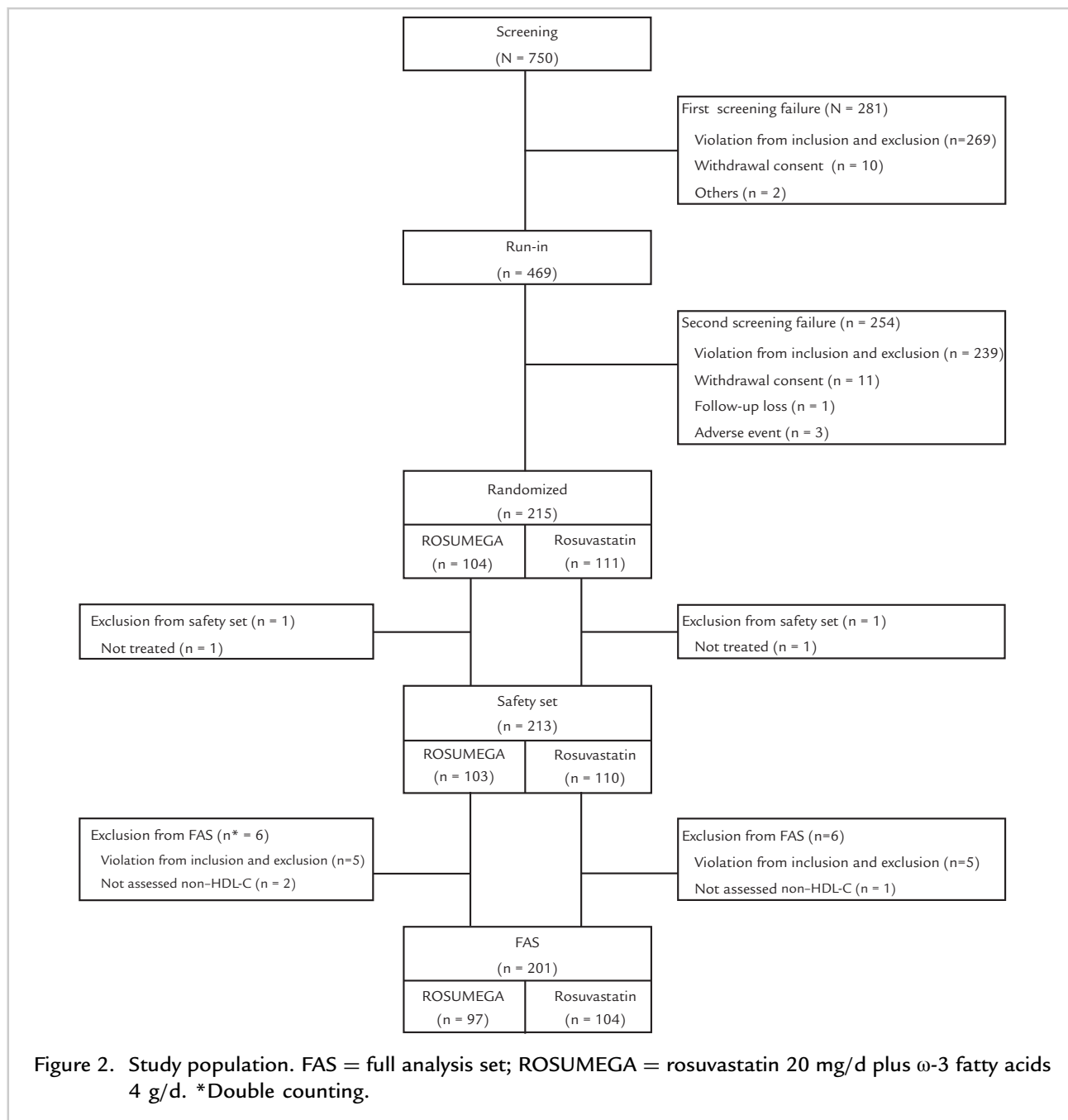
Efficacy End Points

Table II summarizes the results for the changes of lipid and lipoprotein variables. The percentage change at 8 weeks from baseline in TG levels was significantly greater with the ROSUMEGA group compared with the rosuvastatin group (-26.3% vs -11.4% , $P < 0.001$). There was also a greater reduction of non-HDL-C levels in the ROSUMEGA group than in the rosuvastatin group (-10.7% vs -2.2% , $P = 0.001$). Among other lipid parameters, total cholesterol, VLDL-C, Apo A1, and Apo B also had a greater decrease in the ROSUMEGA group than in the rosuvastatin group after 8 weeks of treatment ($P < 0.05$ for each). Meanwhile, LDL-C and HDL-C levels slightly increased after 8 weeks of treatment in both groups, but the difference between the groups was not statistically significant (LDL-C: 1.8% vs 4.3% , $P = 0.335$; HDL-C: 0.9% vs 2.8% , $P = 0.377$).

Subgroup Analysis of Efficacy

We performed subgroup analyses in changes of TG and non-HDL-C levels according to DM, CKD, sex, and age (≥ 65 vs < 65 years). Regardless of the presence of DM, the ROSUMEGA group had a greater reduction in TG levels after 8 weeks compared with the rosuvastatin group (patients with DM: -25.4% vs -9.4% , $P = 0.002$; patients without DM: -29.5% vs -16.8% , $P = 0.045$). This tendency of additional TG-lowering effects of ROSUMEGA was present in both of insulin-dependent DM and non-insulin-dependent DM (insulin-dependent DM: -27.6% vs -14.1% , $P = 0.224$; non-insulin-dependent DM: -24.6% vs -9.4% , $P = 0.011$). Likewise, regardless of CKD, sex, and age groups, greater reductions in TG levels were achieved by the ROSUMEGA group compared with the rosuvastatin group (Figure 3).

In the case of non-HDL-C, the effect of ROSUMEGA on reducing the levels of non-HDL-C after 8 weeks was different by subgroups. In patients with DM, ROSUMEGA had a greater lowering effect on non-HDL-C than rosuvastatin (-12.6% vs -1.6% , $P = 0.002$), but in patients without DM, ROSUMEGA had similar effects on non-HDL-C as rosuvastatin (-4.3% vs -3.8% , $P = 0.250$). Among patients with DM, ROSUMEGA tended to decrease non-HDL-C levels more than rosuvastatin, regardless of insulin dependency (insulin-dependent DM: -19.4% vs $+6.8\%$, $P = 0.018$; non-insulin-dependent DM:



-11.2% vs -4.0%, $P = 0.169$). In the subgroups of normal renal function, female, and elderly (>65 years old), ROSUMEGA had a greater lowering effect on non-HDL-C than rosuvastatin alone (Figure 4).

Clinical Factors That Affect Lipid-lowering Effects of ω -3 Fatty Acids

Multiple linear regression analyses were performed to find the clinical factors associated with the greater

effect of ω -3 fatty acids in lowering TG and non-HDL-C levels. In the case of TGs, the higher the baseline TG level and the lower the body mass index (BMI), the greater the decrease in TGs obtained by adding ω -3 fatty acids. However, DM, age, CKD, and sex did not significantly affect TG reduction (Table III).

Similar to TGs, high baseline non-HDL-C levels and low BMI were associated with a large

Table I. Baseline characteristics.*

Characteristic	ROSUMEGA (n = 97)	Rosuvastatin (n = 104)	P
Age, mean (SD), y	59.7 (10.8)	56.6 (10.5)	0.040
Male	59 (60.8)	67 (64.4)	0.598
Height, mean (SD), cm	162.7 (9.3)	163.1 (8.6)	0.767
Weight, mean (SD), kg	72.5 (12.0)	73.5 (12.4)	0.586
BMI, mean (SD), kg/m ²	27.4 (3.7)	27.6 (3.6)	0.410
Hypertension	75 (77.3)	79 (76.0)	0.820
Diabetes mellitus	75 (77.3)	75 (72.1)	0.397
Insulin-dependent diabetes mellitus	13 (13.4)	17 (16.3)	0.558
Chronic kidney disease	14 (14.4)	15 (14.7)	0.957
Current smoker	25 (25.8)	24 (23.1)	0.656
Alcohol drinking	44 (45.4)	50 (48.1)	0.884
History of coronary artery disease	36 (37.1)	48 (46.2)	0.194
History of cerebrovascular disease	5 (5.2)	7 (6.7)	0.637
10-Year risk score for coronary heart disease	10.5 (6.9)	8.8 (6.5)	0.085
Previous use of statin	90 (92.7)	99 (95.2)	0.471

BMI = body mass index; ROSUMEGA = rosuvastatin 20 mg/d plus ω-3 fatty acids 4 g/d.

*Data are presented as number (percentage) of patients unless otherwise indicated.

non-HDL-C decrease. In addition, the effect of ω-3 fatty acids on reducing non-HDL-C was greater in patients with DM than in patients without

DM. Age, CKD, and sex did not significantly affect non-HDL-C reduction by ω-3 fatty acids (Table IV).

Table II. Lipid and lipoprotein levels at baseline and 8 weeks after treatment.

Variable	ROSUMEGA (n = 97)			Rosuvastatin (n = 104)			P for Percent Change Between Groups
	Baseline, Mean (SD), mg/dL	Week 8, Mean (SD), mg/dL	Percent Change, Mean (SEM)	Baseline, Mean (SD), mg/dL	Week 8, Mean (SD), mg/dL	Percent Change, Mean (SEM)	
Triglycerides	284.0 (68.6)	205.9 (91.4)	-26.3 (3.1)	279.6 (64.2)	241.7 (97.7)	-11.4 (3.4)	<0.001
Non-HDL-C	99.1 (23.7)	86.0 (25.4)	-10.7 (2.9)	96.7 (22.0)	94.1 (30.7)	-2.2 (2.5)	0.001
Total cholesterol	141.2 (24.5)	128.3 (27.2)	-8.1 (1.9)	139.4 (24.0)	137.2 (31.9)	-1.2 (1.7)	<0.001
LDL-C	61.9 (19.6)	61.5 (22.2)	1.8 (3.1)	62.5 (18.4)	64.7 (25.5)	4.3 (2.9)	0.335
HDL-C	42.1 (7.5)	42.3 (8.8)	0.9 (1.5)	42.6 (10.1)	43.1 (8.9)	2.8 (1.6)	0.377
VLDL-C	37.2 (16.4)	24.6 (15.1)	-28.5 (4.4)	34.2 (13.4)	29.4 (19.5)	-12.2 (4.9)	0.004
Apolipoprotein A1	140.1 (23.0)	133.8 (24.5)	-1.5 (4.1)	139.9 (23.8)	138.0 (22.7)	-0.5 (1.2)	0.009
Apolipoprotein B	75.4 (20.5)	71.1 (18.3)	-3.4 (2.5)	75.7 (16.5)	75.3 (20.4)	0.3 (2.0)	0.049

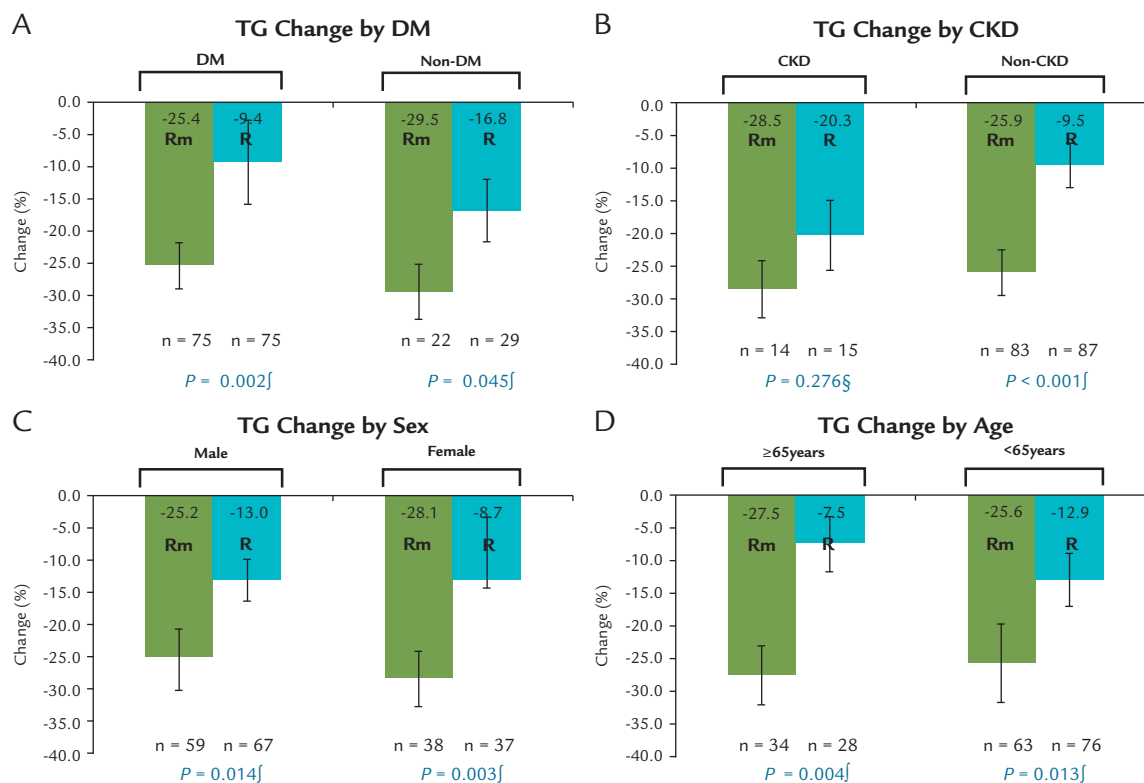


Figure 3. Subgroup analyses in percentage changes of triglyceride (TG) levels after 8 weeks. There was a greater reduction of TG levels in the rosuvastatin 20 mg/d plus ω -3 fatty acids 4 g/d. (ROSUMEGA) group than in the rosuvastatin group regardless of diabetes mellitus (DM), chronic kidney disease (CKD), sex, and age.

Safety analyses

There was no significant difference between groups in adverse events (15.5% in the ROSUMEGA group vs 17.3% in the rosuvastatin group, $P = 0.732$). Serious adverse events occurred in 2 of 103 individuals (1.9%) in the ROSUMEGA group and 2 of 110 (1.8%) in the rosuvastatin group. In particular, the 2 serious adverse events in the ROSUMEGA group were ovarian cancer and parkinsonism, and the 2 serious adverse events in the rosuvastatin group were breast cancer and tarsal tunnel syndrome. None of these were considered related to study treatment. There were no significant increases in creatinine phosphokinase levels (> 5.0 times the upper limit of normal) or alanine aminotransferase levels (> 3.0 times the upper limit of normal) in both groups. One patient in the ROSUMEGA group had mild significant aspartate aminotransferase elevation (> 3.0 times the upper limit of normal)

but < 5 times the upper limit of normal. No adverse drug reactions were observed in the rosuvastatin group.

DISCUSSION

This study found that a combination of ω -3 fatty acids and rosuvastatin in patients with residual hypertriglyceridemia achieved a greater reduction in TG, non-HDL-C, and other lipid and lipoprotein levels than rosuvastatin alone did. In addition, the higher the baseline TG and non-HDL levels and the lower the BMI, the better the effect of ROSUMEGA, and the effect of lowering non-HDL-C levels was more noticeable in patients with DM. Finally, there was no significant adverse event according to adding 4 g/d of ω -3 fatty acids on rosuvastatin.

The most important treatment in patients with dyslipidemia is statins, which mainly lowers LDL-C

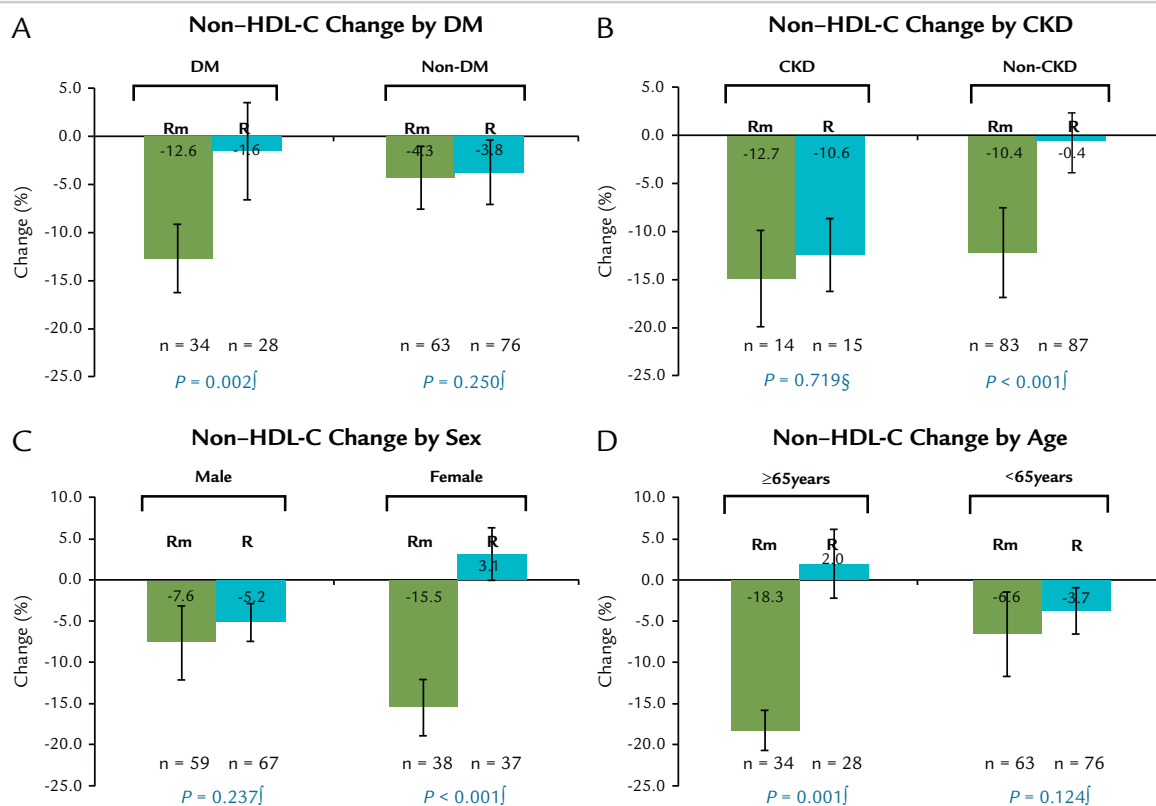


Figure 4. Subgroup analyses in percentage changes of non-HDL-C levels after 8 weeks. rosuvastatin 20 mg/d plus ω -3 fatty acids 4 g/d (ROSUMEGA) found a greater lowering effect on non-HDL-C than rosuvastatin alone in subgroups of patients with diabetes mellitus (DM), patients without chronic kidney disease (CKD), female patients, and elderly patients.

levels. However, statins do not control TG levels effectively. TG levels are classified as normal (<150 mg/dL), borderline (150-199 mg/dL), high (200-499 mg/dL), and very high (\geq 500 mg/dL), and hypertriglyceridemia is defined as TG levels \geq 200 mg/dL, generally. According to Third National Health and Nutrition Examination Survey (NHANES III) in the United States, 35% of men and 25% of women have hypertriglyceridemia (TG \geq 150 mg/dL).¹³ In Korea, the prevalence of hypertriglyceridemia was 38% in men and 20% in women.¹⁴ In patients with DM, the prevalence of hypertriglyceridemia increases, reaching 49%.¹⁴ Hypertriglyceridemia is also known as an independent risk factor associated with cardiovascular event.²⁻⁴ TG is a major component of TG-rich lipoproteins, including VLDL-C and chylomicrons. A recent study suggested that TG is also an independent risk factor for ischemic heart disease.¹⁵ Even non-HDL-C levels were claimed to be

a better predictor of cardiovascular risk than LDL-C.¹⁶ Considering the high prevalence of hypertriglyceridemia and subsequent independent risk for cardiovascular event, TG should also be actively considered in the treatment of dyslipidemia.

Metabolic consequences of hypertriglyceridemia are not well established yet. However, increased TG-rich lipoproteins, a result of hypertriglyceridemia, directly influence composition and metabolism of lipoproteins, making smaller and dense HDL-C and LDL-C particles.¹⁷ This disadvantageously affects cardiovascular disease because hypertriglyceridemic HDL-C (small, dense HDL-C) loses its function to deliver cholesteryl esters¹⁸ and small and dense LDL-C is more susceptible to oxidative modification.¹⁹ In addition, TG-rich lipoproteins have atherogenic effects by inducing macrophage dysfunction, endothelial cell inflammation, and coagulation abnormality.¹⁷

Table III. Predictive model for reduction in TGs by ω -3 fatty acids.*

Variable	Reduction of TGs, mg/dL (95% CI)	P
Higher baseline TG level (by 10-mg/dL increment)	5.4 (2.8 to 8.0)	<0.001
Lower BMI (by 1-kg/m ² decrement)	5.3 (0.2 to 10.4)	0.041
Non-DM (vs DM)	14.3 (-28.7 to 57.3)	0.510
Younger age (by 10-year decrement)	8.9 (-10.3 to 28.1)	0.360
CKD (vs non-CKD)	32.6 (-24.1 to 89.3)	0.256
Female (vs. male)	27.0 (-13.0 to 66.9)	0.183

BMI = body mass index, CKD = chronic kidney disease, DM = diabetes mellitus, TG = triglyceride.

*TG level reduction after adding ω -3 fatty acids compared with rosuvastatin treatment during the run-in period was estimated by linear regression analysis. The coefficient of determination (R^2) of the model was 21.3% ($P = 0.001$).

Treatment options for reducing TG levels include ω -3 fatty acids, niacin, and fibrates. However, niacin causes flushing, liver toxic effects, and myopathy and has the risk to increase serum glucose, especially when coadministered with a statin.²⁰ Fibrates also has a risk of myopathy and the potential to blunt the beneficial effect of statins.²¹ Therefore, only ω -3 fatty acids are available to use for reducing TG levels without burdens of additional adverse effects.

Historically, ω -3 fatty acids suggested its benefit in observational studies, reporting that intake of ω -3 fatty acid-enriched food reduced cardiovascular risk.²² The TG-lowering mechanisms of ω -3 fatty acids are direct inhibition of TG synthesis, reduction of hepatic synthesis of VLDL-Apo B, stimulation of fatty acid oxidation, and enhancing TG clearance with increased plasma lipolytic activity.²³ Currently used

concentrated forms of ω -3 fatty acids include eicosapentaenoic acid and docosahexaenoic acid, which have similar TG reduction ranges to each other (eicosapentaenoic acid: +1.8% to -34.9%; docosahexaenoic acid: -8.0% to -43.7%).²⁴ TG-lowering effects of ω -3 fatty acids are dependent on baseline TG levels. The higher the baseline TG level, the greater the TG-lowering effect of ω -3 fatty acids. In previous randomized controlled trials, 2 and 4 g/d of ω -3 fatty acids had a reduction of TG levels of 20% to 26% and 31% to 33%, respectively, in patients with severe hyperglyceridemia of TG levels ≥ 500 mg/dL.^{25,26} In case of hyperglyceridemia with a TG level < 500 mg/dL, several studies have compared a combination of ω -3 fatty acids and statin with statin alone. A combination of ω -3 fatty acids 4 mg/d with simvastatin 40 mg/d for 8 weeks produced a greater

Table IV. Predictive model for reduction in non-HDL-C by ω -3 fatty acids.*

Variable	Reduction of Non-HDL-C, mg/dL (95% CI)	P
Higher baseline non-HDL-C (by 10-mg/dL increment)	5.7 (3.8 to 7.7)	<0.001
Lower BMI (by 1-kg/m ² decrement)	1.6 (0.3 to 2.9)	0.015
DM (vs non-DM)	14.3 (3.2 to 25.5)	0.012
Younger age (by 10-year decrement)	1.3 (-3.6 to 6.2)	0.597
CKD (vs non-CKD)	7.0 (-7.4 to 21.5)	0.337
Female (vs male)	5.1 (-5.1 to 15.3)	0.322

BMI = body mass index, CKD = chronic kidney disease, DM = diabetes mellitus.

*Non-HDL-C level reduction after adding ω -3 fatty acids compared with rosuvastatin treatment during the run-in period was estimated by linear regression analysis. The coefficient of determination (R^2) of the model was 33.5% ($P < 0.001$).

reduction in TG levels by 30% and non-HDL-C levels by 9%, whereas simvastatin alone reduces TG levels by 6% and non-HDL-C levels by 2%.⁸ In another randomized study, ω -3 fatty acids 4 g/d combined with several kinds of statins also reduced TG levels by a greater amount than statin alone (18% vs 6%).²⁷ In our study, the percentage changes from baseline TG and non-HDL-C were significantly greater in the ROSUMEGA group than in the rosuvastatin group (TG: -26.3% vs -11.4%, $P < 0.001$; non-HDL-C: -10.7% vs -2.2%, $P = 0.001$), which are consistent with the results of previous studies. These results suggest that ω -3 fatty acids have definitely additive and complementary effects on TG and non-HDL-C control with different mechanisms. As in our study, LDL-C levels were mildly increased in previous studies of ω -3 fatty acids. ω -3 fatty acids reduce VLDL-C secretion from liver; as a result, the level of LDL-C is slightly increased by the process of converting VLDL-C to LDL-C.²⁸ Although LDL-C increases, it is less harmful because the larger and less atherosclerotic LDL-C subcomponent mainly increases.²³

In subgroup analyses, we can notice that additive TG-lowering effects of ω -3 fatty acids are observed regardless of DM, CKD, sex, and age. Therefore, ω -3 fatty acids can be applied to any clinical setting of hypertriglyceridemia. However, in terms of non-HDL-C, a combination of ω -3 fatty acids with rosuvastatin had different effects in each subgroup compared with rosuvastatin alone. There was a more prominent non-HDL-C-lowering effect of ROSUMEGA in patients with DM, normal renal function, female, and older age. In addition, further TG and non-HDL-C-lowering effects of ω -3 fatty acids in DM were observed regardless of insulin dependency.

In multiple linear regression analyses, the effect of ω -3 fatty acids on TG reduction was greater with higher baseline TG levels and lower BMI. Similarly, in non-HDL-C, the higher the baseline non-HDL-C level and the lower the BMI, the greater the non-HDL-C reduction. Previous studies have found that the higher the baseline lipid level, the greater the reduction in ω -3 fatty acids.²⁹ In addition, our results suggest that lowering weight and maintaining adequate BMI may be helpful in controlling TG and non-HDL-C levels. Interestingly, the effect of ω -3 fatty acids in lowering non-HDL-C levels is greater

in patients with DM, although TG reduction is not affected by the presence of DM. Non-HDL-C is a more inclusive measure of all atherogenic Apo B-containing lipoproteins: VLDL-C, IDL-C, chylomicron remnants, lipoprotein A, and LDL-C.³⁰ Non-HDL-C is known to be particularly elevated in patients with DM³¹ and serves as a strong predictor of cardiovascular disease in patients with DM.³² Therefore, our results, which report the obvious non-HDL-C-reducing effect of ROSUMEGA in patients with DM, emphasize that the addition of ω -3 fatty acids should be considered in patients with DM.

Rosuvastatin has proven to be more potent than any other statins in many randomized controlled trials.³³⁻³⁵ However, the combination of rosuvastatin and ω -3 fatty acids has not been previously studied. Our study was the first to examine the effect of adding ω -3 fatty acids to rosuvastatin and proved an additive effect of adding ω -3 fatty acids to rosuvastatin on reducing TG levels, without any significant adverse event.

However, the present study has several limitations. First, the duration of treatment was short. Additional long-term studies on the efficacy and tolerability of ω -3 fatty acids are needed. It is also necessary to study whether the reduction in TG levels using ω -3 fatty acids is preventing cardiovascular events. Nevertheless, this study proved that even short-term treatment with ω -3 fatty acids effectively reduced TG and non-HDL-C levels. Second, the study population was exclusively middle-aged Asians, which limits the generalizability of the results. Third, there were age differences in baseline characteristics between the ROSUMEGA and rosuvastatin groups. However, in the subgroup analysis, ROSUMEGA had a tendency to lower TG and non-HDL-C levels more than rosuvastatin regardless of age group. In addition, age was not a significant independent variable in multiple linear regression analyses of the ROSUMEGA effect, so the age difference between the 2 study groups was determined to be acceptable.

CONCLUSIONS

In patients with residual hypertriglyceridemia despite statin treatment, a combination of ω -3 fatty acids and rosuvastatin decreases TG and non-HDL-C levels to a

greater extent than rosuvastatin alone. Further study is needed to determine whether the advantages of this lipid profile of ω -3 fatty acids actually leads to the prevention of cardiovascular event.

ACKNOWLEDGMENTS

Hyo-Soo Kim contributed to the study conception and design with Sang Hak Lee, Hui Kyung Jeon, Sang Hyun Kim, Ki Hoon Han, Young Joon Hong, and Jidong Sung. All the authors, except Chee Hae Kim, contributed to data collection and interpretation of data. All authors confirmed the final version of the article. Chee Hae Kim and Hyo-Soo Kim contributed to writing, analysis, and interpretation of data.

FUNDING SOURCES

This study was funded by the Kuhnil Pharmaceutical Co Ltd.

CONFLICTS OF INTEREST

The authors have indicated that they have no conflicts of interest regarding the content of this article.

REFERENCES

1. Ray KK, Kastelein JJ, Boekholdt SM, et al. The ACC/AHA 2013 guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular disease risk in adults: the good the bad and the uncertain: a comparison with ESC/EAS guidelines for the management of dyslipidaemias 2011. *Eur Heart J*. 2014;35:960–968.
2. Freiberg JJ, Tybjaerg-Hansen A, Jensen JS, Nordestgaard BG. Nonfasting triglycerides and risk of ischemic stroke in the general population. *JAMA*. 2008;300:2142–2152.
3. Labreuche J, Touboul P-J, Amarenco P. Plasma triglyceride levels and risk of stroke and carotid atherosclerosis: a systematic review of the epidemiological studies. *Atherosclerosis*. 2009;203:331–345.
4. Sarwar N, Danesh J, Eiriksdottir G, et al. Triglycerides and the risk of coronary heart disease 10,158 incident cases among 262,525 participants in 29 western prospective studies. *Circulation*. 2007;115:450–458.
5. Chapman MJ, Ginsberg HN, Amarenco P, et al, European Atherosclerosis Society Consensus Panel. Triglyceride-rich lipoproteins and high-density lipoprotein cholesterol in patients at high risk of cardiovascular disease: evidence and guidance for management. *Eur Heart J*. 2011;32:1345–1361.
6. Harris WS, Ginsberg HN, Arunakul N, et al. Safety and efficacy of Omacor in severe hypertriglyceridemia. *J Cardiovasc Risk*. 1997;4:385–391.
7. Maki KC, Lawless AL, Kelley KM, et al. Effects of prescription omega-3-acid ethyl esters on fasting lipid profile in subjects with primary hypercholesterolemia. *J Cardiovasc Pharmacol*. 2011;57:489–494.
8. Davidson MH, Stein EA, Bays HE, et al. COMBination of prescription Omega-3 with Simvastatin (COMBOS) Investigators. 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.
9. Dunbar RL, Nicholls SJ, Maki KC, et al. Effects of omega-3 carboxylic acids on lipoprotein particles and other cardiovascular risk markers in high-risk statin-treated patients with residual hypertriglyceridemia: a randomized, controlled, double-blind trial. *Lipids Health Dis*. 2015;14:1.
10. Ng TW, Ooi EM, Watts GF, et al. Atorvastatin plus omega-3 fatty acid ethyl ester decreases very-low-density lipoprotein triglyceride production in insulin resistant obese men. *Diabetes Obes Metab*. 2014;16:519–526.
11. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive summary of the Third Report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III). *JAMA*. 2001;285:2486–2497.
12. Eknoyan G, Lameire N, Eckardt K, et al. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney Int*. 2013;3:5–14.
13. Alexander CM, Landsman PB, Teutsch SM, Haffner SM. NCEP-defined metabolic syndrome, diabetes, and prevalence of coronary heart disease among NHANES III participants age 50 years and older. *Diabetes*. 2003;52:1210–1214.
14. Roh E, Ko SH, Kwon HS, et al, Taskforce Team of Diabetes Fact Sheet of the Korean Diabetes Association. Prevalence and management of dyslipidemia in Korea: Korea National Health and Nutrition Examination Survey during 1998 to 2010. *Diabetes Metab J*. 2013;37:433–449.
15. Varbo A, Benn M, Tybjaerg-Hansen A, et al. Remnant cholesterol as a causal risk factor for ischemic heart disease. *J Am Coll Cardiol*. 2013;61:427–436.
16. Di Angelantonio E, Sarwar N, Perry P, et al. Major lipids, apolipoproteins, and risk of vascular disease. *JAMA*. 2009;302:1993–2000.
17. Miller M, Stone NJ, Ballantyne C, et al. Triglycerides and cardiovascular disease a scientific statement from the American Heart Association. *Circulation*. 2011;123:2292–2333.

18. Greene DJ, Skeggs JW, Morton RE. Elevated triglyceride content diminishes the capacity of high density lipoprotein to deliver cholesteryl esters via the scavenger receptor class B type I (SR-BI). *J Biol Chem.* 2001; 276:4804–4811.
19. Chait A, Brazg RL, Tribble DL, Krauss RM. Susceptibility of small, dense, low-density lipoproteins to oxidative modification in subjects with the atherogenic lipoprotein phenotype, pattern B. *Am J Med.* 1993;94:350–356.
20. Ito MK. Long-chain omega-3 fatty acids, fibrates and niacin as therapeutic options in the treatment of hypertriglyceridemia: a review of the literature. *Atherosclerosis.* 2015;242: 647–656.
21. Davidson MH, Rosenson RS, Maki KC, et al. Effects of Fenofibric Acid on Carotid Intima-Media Thickness in Patients With Mixed Dyslipidemia on Atorvastatin Therapy Randomized, Placebo-Controlled Study (FIRST). *Arterioscler Thromb Vasc Biol.* 2014;34:1298–1306.
22. Kris-Etherton PM, Harris WS, Appel LJ, Committee N. Fish consumption, fish oil, omega-3 fatty acids, and cardiovascular disease. *Circulation.* 2002;106:2747–2757.
23. Jacobson TA. Role of n-3 fatty acids in the treatment of hypertriglyceridemia and cardiovascular disease. *Am J Clin Nutr.* 2008;87: 1981S–1990S.
24. Jacobson TA, Glickstein SB, Rowe JD, Soni PN. Effects of eicosapentaenoic acid and docosahexaenoic acid on low-density lipoprotein cholesterol and other lipids: a review. *J Clin Lipidol.* 2012;6: 5–18.
25. Maki KC 1, Orloff DG, Nicholls SJ, et al. A highly bioavailable omega-3 free fatty acid formulation improves the cardiovascular risk profile in high-risk, statin-treated patients with residual hypertriglyceridemia (the ESPRIT trial). *Clin Ther.* 2013; 35:1400–1411.
26. Bays HE, Ballantyne CM, Kastelein JJ, et al. Eicosapentaenoic acid ethyl ester (AMR101) therapy in patients with very high triglyceride levels (from the Multi-center, placebo-controlled, Randomized, double-blind, 12-week study with an open-label Extension [MARINE] trial). *Am J Cardiol.* 2011;108: 682–690.
27. Ballantyne CM 1, Bays HE, Kastelein JJ, et al. Efficacy and safety of eicosapentaenoic acid ethyl ester (AMR101) therapy in statin-treated patients with persistent high triglycerides (from the ANCHOR study). *Am J Cardiol.* 2012;110:984–992.
28. Chan DC, Watts GF. Dyslipidaemia in the metabolic syndrome and type 2 diabetes: pathogenesis, priorities, pharmacotherapies. *Expert Opin Pharmacother.* 2011;12:13–30.
29. Pirillo A, Catapano AL. Omega-3 polyunsaturated fatty acids in the treatment of hypertriglyceridaemia. *Int J Cardiol.* 2013;170:S16cS20.
30. Blaha MJ, Blumenthal RS, Brinton EA, Jacobson TA, National Lipid Association Taskforce on Non-HDL Cholesterol. The importance of non-HDL cholesterol reporting in lipid management. *J Clin Lipidol.* 2008; 2:267–273.
31. Sniderman AD, Scantlebury T, Cianflone K. Hypertriglyceridemic hyperapob: the unappreciated atherogenic dyslipoproteinemia in type 2 diabetes mellitus. *Ann Intern Med.* 2001;135: 447–459.
32. Lu W, Resnick HE, Jablonski KA, et al. Non-HDL cholesterol as a predictor of cardiovascular disease in type 2 diabetes. *Diabetes Care.* 2003;26:16–23.
33. Jones PH, Davidson MH, Stein EA, et al. Comparison of the efficacy and safety of rosuvastatin versus atorvastatin, simvastatin, and pravastatin across doses (STELLAR Trial). *Am J Cardiol.* 2003;92:152–160.
34. Strandberg TE, Feely J, Sigurdsson EL. Twelve-week, multicenter, randomized, open-label comparison of the effects of rosuvastatin 10 mg/d and atorvastatin 10 mg/d in high-risk adults: a DISCOVERY study. *Clin Ther.* 2004; 26:1821–1833.
35. Olsson AG, Istad H, Luurila O, et al. Effects of rosuvastatin and atorvastatin compared over 52 weeks of treatment in patients with hypercholesterolemia. *Am Heart J.* 2002;144:1044–1051.

Address correspondence to: Hyo-Soo Kim, MD, PhD, Department of Internal Medicine, Seoul National University Hospital, Cardiovascular Centre, 101 Daehak-ro, Jongro-gu, Seoul 110-744, Korea. E-mail: usahyosoo@gmail.com, hyosoo@snu.ac.kr