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# Statin/ezetimibe combination therapy vs statin monotherapy for carotid atherosclerotic plaque inflammation

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**Abstract**

It remains uncertain whether statin/ezetimibe combination therapy serves as a useful and equivalent alternative to statin monotherapy for reducing atherosclerotic plaque inflammation. The aim of the present study was to compare the effects of statin/ezetimibe combination therapy and statin monotherapy on carotid atherosclerotic plaque inflammation using $^{18}$F-fluorodeoxyglucose ($^{18}$FDG) positron emission tomography (PET)/computed tomography (CT) imaging. Data were pooled from 2 clinical trials that used serial $^{18}$FDG PET/CT examination to investigate the effects of cholesterol-lowering therapy on carotid atherosclerotic plaque inflammation. The primary outcome was the percent change in the target-to-background ratio (TBR) of the index vessel in the most diseased segment (MDS) at 6-month follow-up. Baseline characteristics were largely similar between the 2 groups. At the 6-month follow-up, the MDS TBR of the index vessel significantly decreased in both groups. The percent change in the MDS TBR of the index vessel (primary outcome) did not differ significantly between the 2 groups (−8.41 ± 15.9% vs −8.08 ± 17.0%, respectively, $P = .936$). Likewise, the percent change in the whole vessel TBR of the index vessel did not differ significantly between the 2 groups. There were significant decreases in total and LDL cholesterol levels in both groups at follow-up ($P < .001$). There were no significant correlations between the percent changes in MDS TBR of the index vessel, changes in the lipid, and high-sensitive C-reactive protein levels. The reduction in carotid atherosclerotic plaque inflammation by statin/ezetimibe combination therapy was equivalent to that by the statin monotherapy.

**Abbreviations:** $^{18}$FDG = $^{18}$F-fluorodeoxyglucose, ASCVD = atherosclerotic cardiovascular disease, CT = computed tomography, CTT = Cholesterol Treatment Trialists', HDL-C = high-density lipoprotein cholesterol, LDL-C = low-density lipoprotein cholesterol, MDS = most diseased segment, PET = positron emission tomography, ROI = region of interest, SUV = standardized uptake value, TBR = target-to-background ratio.

**Keywords:** ezetimibe, plaque inflammation, positron emission tomography, statin

## 1. Introduction

Statins remain the first-line therapy to prevent cardiovascular events in patients with atherosclerotic cardiovascular disease (ASCVD). The benefits of statin therapy depend on the magnitude of low-density lipoprotein cholesterol (LDL-C) lowering, and have no lower threshold limit at which LDL-C lowering is not beneficial.[1,2] Furthermore, statin therapy slows the progression of atherosclerosis, and may even lead to atherosclerotic plaque

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*Written informed consent was obtained from all individual participants included in the study.*

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*The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.*

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regression.[3–5] Current guidelines recommend moderate- or high-intensity statin therapy for the prevention of cardiovascular events according to the baseline ASCVD risk.[6,7]

Statins are generally well tolerated across the clinically recommended dose range. However, statin-associated muscle symptoms including myalgia and weakness are not uncommon, and are usually dose dependent.[8,9] Inflammation is the key reaction leading to plaque instability, and statins are believed to induce plaque stabilization by exerting anti-inflammatory effects.[10–12] The beneficial effects of LDL-C lowering therapy might not depend on the methods by which LDL-C is reduced.[13] Therefore, to minimize side effects, combination therapy with low-intensity statins and ezetimibe is often used as an alternative to moderate- or high-intensity statins.[14,15] Although these approaches have shown a similar reduction in LDL-C levels, a limited number of studies have compared their effects on atherosclerotic plaque inflammation. $^{18}$F-fluorodeoxyglucose ($^{18}$FDG) uptake in the aorta and the carotid arteries reflects atherosclerotic plaque inflammation, and can be used to monitor the efficacy of LDL-C lowering therapy.[16]

In this study, we compared the 2 approaches of LDL-C lowering therapy on carotid atherosclerotic plaque inflammation using $^{18}$FDG positron emission tomography (PET)/computed tomography (CT) imaging.

## 2. Methods

### 2.1. Study design

The present study included patients with acute coronary syndrome who participated in 2 clinical trials that assessed the effects of cholesterol-lowering therapy on carotid atherosclerotic plaque inflammation. Acute coronary syndrome including ST-segment elevation myocardial infarction, non-ST-segment elevation myocardial infarction, and unstable angina was diagnosed based on the clinical symptoms, electrocardiography, and a rise in troponins. The trials used a common protocol with the only exception being the cholesterol-lowering medications; the effects of simvastatin/ezetimibe 10 mg/10 mg vs rosuvastatin 10 mg,[17] and rosuvastatin/ezetimibe 5 mg/10 mg vs rosuvastatin 20 mg on carotid atherosclerotic plaque inflammation were compared.[18] In each of these studies, patients were required to have carotid artery disease (diameter of stenosis, 20%–50%), acute coronary syndrome, and at least one carotid $^{18}$FDG uptake lesion (target-to-background ratio (TBR) $\geq$ 1.6). Exclusion criteria included the following:

1. a previous history of carotid endarterectomy or stenting;
2. scheduled cardiac or major surgery within the next 6 months;
3. an ezetimibe or statin in the past 4 weeks;
4. chronic disease that required treatment with oral, intravenous, or intraarticular steroids;
5. end-stage renal disease;
6. chronic liver disease;
7. a history of cancer within the past 3 years;
8. pregnant/breast-feeding or of child-bearing potential; and
9. a life expectancy <2 years.

### 2.2. Database pooling

The datasets of individual trials were merged and checked for consistency and completeness by a study investigator. The merged database included information on patient demographics, risk factors (current smoker, diabetes, hypertension, family history of coronary artery disease [<55 years in men and <65 years in women, first degree relatives]), clinical history, laboratory findings, medications, and 18FDG PET/CT data. 18FDG PET/CT examinations and biochemical laboratory tests were performed at baseline and 6 months after randomization. The protocol for each study was approved by the Institutional Review Committee of Asan Medical Center (IRB No. 2015–0194, 2017–0160) and Korea University Guro Hospital (IRB No. 2017GR0373), and written informed consent was obtained from all participants.

### 2.3. Image analysis

The acquisition and analysis of $^{18}$FDG PET/CT images has been described in detail previously.[16,19] Briefly, we visually evaluated the focal $^{18}$FDG activity in the bilateral carotid arteries and the ascending aorta. A circular region of interest (ROI) was drawn around the vascular wall and the maximal standardized uptake value (SUV) of each ROI was recorded. The TBR was the ratio of the SUVs of each vessel and the superior vena cava. The TBR of the most diseased segment (MDS) of each vessel was measured by centering on the slice showing the highest $^{18}$FDG activity and then averaging contiguous superior and inferior segments of about 1.5 cm.

### 2.4. Study outcomes

The primary outcome was the percent change in MDS TBR of the index vessel defined as (MDS TBR at 6 months–MDS TBR at baseline)/(MDS TBR at baseline) $\times$ 100. The secondary outcomes were changes in the whole vessel TBR within the index vessel, MDS TBR, and whole vessel TBR of the aorta, lipid profiles, and high sensitive C-reactive protein levels.

### 2.5. Statistical analysis

Continuous variables were reported as mean $\pm$ standard deviation, and categorical variables as frequencies. Continuous variables were compared using the paired $t$ test or Wilcoxon signed rank test for changes within groups, and the unpaired $t$ test or Mann–Whitney $U$ test for differences between groups. Categorical variables were compared between groups using Chi-Squared test or Fisher exact test.

A linear mixed effect model was used for comparison between groups. The linear mixed effect models adopted here were one-stage approaches to analyze pooled individual patient data; this included the study trial because random effects accounted for the clustering effect of patients with studies, and the between-trial variance could not be captured by covariates. Subgroup analysis of the primary outcome was conducted for the following variables: age, sex, diagnosis, baseline LDL-C, baseline hs-CRP, baseline TBR, and regimens. Subgroup by treatment interactions were tested using this model.

SPSS version 21 (IBM) and SAS version 9.4 (SAS Institute, Cary, NC) were used for all statistical analyses. A two-sided $P < .05$ was considered statistically significant.

## 3. Results

### 3.1. Baseline characteristics

The baseline demographics, clinical characteristics, and medication use in each of the treatment groups are summarized in

**Table 1**

**Baseline clinical characteristics.**

| Characteristics | Statin/ezetimibe (n = 48) | Statin (n = 50) | *P* value |
|---|---|---|---|
| Age (years) | 60.9 ± 8.7 | 59.2 ± 9.2 | .332 |
| Male | 42 (87.5%) | 44 (88.0%) | .940 |
| Current smoker | 13 (27.1%) | 14 (28.0%) | .919 |
| Diabetes mellitus | 6 (12.5%) | 8 (16.0%) | .621 |
| Hypertension | 28 (58.3%) | 17 (34.0%) | .016 |
| Diagnosis | | | .580 |
| STEMI | 36 (75.0%) | 35 (70.0%) | |
| NSTE-ACS | 12 (25.0%) | 15 (30.0%) | |
| Culprit artery of ACS | | | .174 |
| Left anterior descending coronary | 24 (50.0%) | 32 (64.0%) | |
| Left circumflex coronary | 6 (12.5%) | 2 (4.0%)) | |
| Right coronary | 18 (37.5%) | 14 (28.0%) | |
| Ramus intermedius | 0 (0.0%) | 1 (2.0%) | |
| Left main | 0 (0.0%) | 1 (2.0%) | |
| Culprit lesion PCI | 34 (72.3%) | 35 (71.4%) | .921 |
| Left ventricular ejection fraction (%) | 53.4 ± 8.0 | 53.7 ± 8.0 | .920 |
| Medication at the time of follow-up | | | |
| Aspirin | 48 (100.0%) | 50 (100.0%) | >.999 |
| P2Y12 inhibitors | 48 (100.0%) | 50 (100.0%) | >.999 |
| β-blockers | 38 (79.2%) | 35 (70.0%) | .298 |
| Angiotensin II receptor blocker | 23 (47.9%) | 26 (52.0%) | .686 |
| Calcium channel blocker | 17 (35.4%) | 19 (38.0%) | .791 |

ACS = acute coronary syndrome, NSTE-ACS = non-ST-segment elevation-acute coronary syndrome, PCI = percutaneous coronary intervention, STEMI = ST-segment elevation myocardial infarction.

Table 1. Patients in the statin/ezetimibe combination therapy group took simvastatin/ezetimibe 10 mg/10 mg (n = 25) or rosuvastatin/ezetimibe 5 mg/10 mg (n = 23), and those in the statin monotherapy group took rosuvastatin 10 mg (n = 25) or rosuvastatin 20 mg (n = 25). There were no significant differences in baseline characteristics between the 2 groups. The mean age of the patients was 60.0 ± 8.9 years, and a total of 87.8% were men. On admission, 27.6% of patients received a diagnosis of non-ST-segment elevation acute coronary syndrome, and 72.4% received a diagnosis of ST-segment elevation myocardial infarction.

### 3.2. Laboratory findings

Table 2 shows the laboratory biochemical measures at baseline and 6-month follow-up. The baseline laboratory findings were largely similar between the 2 groups. At the 6-month follow-up, the total cholesterol and LDL-C levels were significantly decreased in both groups ($P < .001$). A similar proportion of patients achieved LDL-C levels below 70 mg/dl (40.4% in the statin/ezetimibe group vs 50.0% in the statin group, $P = .344$) in both groups. There were no significant changes in HDL cholesterol (HDL-C) and triglyceride levels in both groups. The high-sensitive C-reactive protein levels at follow-up were 0.1 ± 0.1 mg/dl in the statin/ezetimibe group and 0.2 ± 0.3 mg/dl in the statin group ($P = .400$).

### 3.3. End points

Table 3 summarizes the baseline and changes in the $^{18}$FDG PET/CT parameters of each treatment group. The MDS TBR of the index vessel, whole vessel TBR within the index vessel, and the TBR of the aorta at baseline did not differ significantly between the 2 groups. At 6-month follow-up, the MDS TBR of the index vessel significantly decreased in both groups. Figure 1 shows representative images. The percent change in the MDS TBR of the index vessel (primary endpoint) did not differ significantly between the 2 groups (−8.41 ± 15.9% in the statin/ezetimibe group vs −8.08 ± 17.0% in the statin group, $P = .936$) (Fig. 2). Likewise, the percent change in the whole vessel TBR of the index vessel did not differ significantly between the 2 groups. Furthermore, no significant interaction was found between the treatment effects and baseline MDS TBR values, LDL-C levels,

**Table 2**

**Laboratory findings.**

| Characteristics | Statin/ezetimibe (n = 48) | Statin (n = 50) | *P* value |
|---|---|---|---|
| Total cholesterol (mg/dl) | | | |
| Baseline | 178.8 ± 36.5 | 180.6 ± 39.3 | .820 |
| 6 months | 131.0 ± 24.2 | 125.8 ± 21.5 | .267 |
| Triglyceride (mg/dl) | | | |
| Baseline | 116.7 ± 59.5 | 121.3 ± 67.8 | .721 |
| 6 months | 118.9 ± 52.4 | 112.9 ± 46.2 | .550 |
| LDL-C (mg/dl) | | | |
| Baseline | 121.4 ± 34.2 | 123.6 ± 37.0 | .764 |
| 6 months | 79.3 ± 21.0 | 74.0 ± 19.7 | .205 |
| HDL-C (mg/dl) | | | |
| Baseline | 45.0 ± 9.8 | 45.9 ± 12.0 | .673 |
| 6 months | 45.8 ± 8.0 | 46.0 ± 9.5 | .906 |
| Hs-CRP (mg/L) | | | |
| Baseline | 0.5 ± 1.1 | 0.4 ± 0.6 | .364 |
| months | 0.1 ± 0.1 | 0.2 ± 0.3 | .400 |

HDL-C = high-density lipoprotein cholesterol, Hs-CRP = high sensitivity C-reactive protein, LDL-C = low-density lipoprotein cholesterol.

**Table 3**

**Changes in arterial inflammation activity.**

| Characteristics | Statin/ezetimibe (n = 48) | Statin (n = 50) | *P* value between groups |
|---|---|---|---|
| MDS TBR of index carotid artery | | | |
| Baseline | 2.3 ± 0.5 | 2.3 ± 0.4 | .849 |
| Follow-up | 2.1 ± 0.4 | 2.1 ± 0.4 | .740 |
| Nominal change | −0.2 ± 0.4 | −0.2 ± 0.4 | .895 |
| *P* value compared to baseline | <.001 | .001 | |
| Percent change (primary endpoint) | −8.4 ± 16.0 | −8.1 ± 17.0 | . 936 |
| Whole vessel TBR of index carotid artery | | | |
| Baseline | 2.0 ± 0.4 | 2.0 ± 0.3 | .986 |
| Follow-up | 1.8 ± 0.3 | 1.8 ± 0.3 | .937 |
| Nominal change | −0.2 ± 0.3 | −0.2 ± 0.3 | .951 |
| *P* value compared with baseline | <.001 | <.001 | |
| Percent change | −7.6 ± 16.1 | −7.9 ± 14.4 | .933 |
| MDS TBR of aorta | | | |
| Baseline | 2.6 ± 0.6 | 2.6 ± 0.5 | .936 |
| Follow-up | 2.3 ± 0.4 | 2.3 ± 0.4 | .502 |
| Nominal change | −0.3 ± 0.5 | −0.2 ± 0.4 | .578 |
| *P* value compared with baseline | <.001 | <.001 | |
| Percent change | −10.0 ± 17.0 | −8.2 ± 15.6 | .683 |
| Whole vessel TBR of aorta | | | |
| Baseline | 2.4 ± 0.5 | 2.4 ± 0.4 | .865 |
| Follow-up | 2.1 ± 0.4 | 2.2 ± 0.4 | .491 |
| Nominal change | −0.3 ± 0.4 | −0.2 ± 0.4 | .606 |
| *P* value compared to baseline | <.001 | <.001 | |
| Percent change | −9.7 ± 16.1 | −7.6 ± 15.9 | .617 |

Nominal change was calculated as follow-up minus baseline, and percent change was calculated as (follow-up minus baseline)/baseline × 100.
MDS = most diseased segment, TBR = tissue blood ratio.

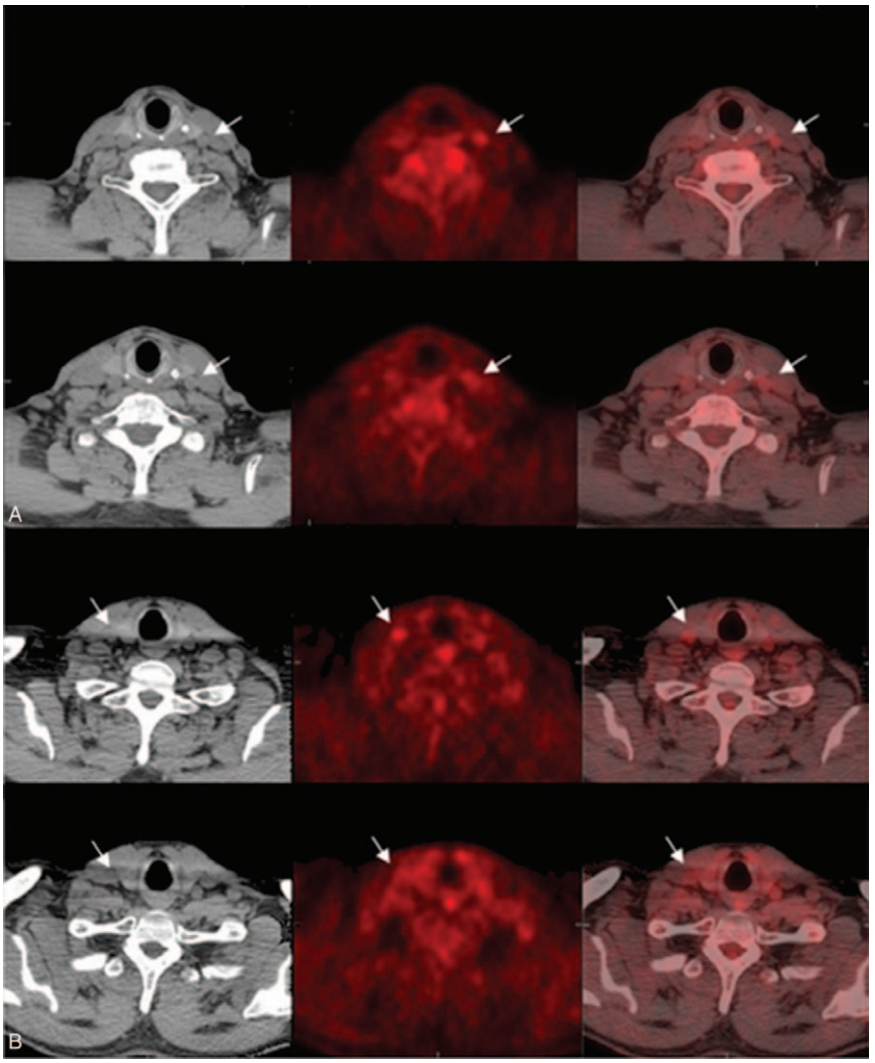


**Figure 1.** CT (left), FDG PET (middle), and FDG PET/CT (right) at baseline (the first and third rows) and 6-month follow-up (the second and fourth rows) after statin/ezetimibe (A) and statin (B) treatment. Uptake by carotid arteries (arrows) decreased after treatment in both groups.

and clinical diagnosis with respect to the primary endpoint (Fig. 3). Similar results were observed for changes in the MDS TBR and the whole vessel TBR of the aorta (Table 3). Significant correlations were not found between percent changes in MDS TBR of the index vessel, changes in the lipid, and high-sensitive C-reactive protein levels.

## 4. Discussion

In this pooled analysis of patients with mild carotid atherosclerosis and acute coronary syndrome, we found that atherosclerotic plaque inflammation of the carotid artery and aorta evaluated by $^{18}$FDG PET/CT imaging decreased in both the statin/ezetimibe combination therapy and statin monotherapy groups. The 2 treatment groups did not differ significantly in terms of the degree of improvement across various subgroups. In addition, the lipid profiles and C-reactive protein levels were similarly improved in both groups, with no associations between changes in inflammation and on treatment lipid or C-reactive protein levels. These findings support that statin/ezetimibe combination therapy offers anti-inflammatory effects similar to statin monotherapy at equivalent **LDL-C**-lowering doses.

Inflammation is involved in all stages of the atherosclerotic process, including plaque development, progression, and destabilization.[20] Inflammation destroys the fibrous cap with thrombus formation, leading to acute coronary syndrome or stroke. Advances in PET imaging make it possible to visualize atherosclerotic plaque inflammation of the carotid artery and aorta. $^{18}$F-FDG is a radiolabeled glucose analogue that is taken up by active macrophages with the accumulation being proportional to metabolic demands, reflecting the inflammatory activity of macrophages.[16]$^{18}$F-FDG represents a reliable and reproducible method to evaluate atherosclerotic plaque inflammation that can be used as a surrogate marker of antiatherosclerotic therapies.[19] Cholesterol lowering drugs, including statins and ezetimibe, are believed to reduce atherosclerotic plaque inflammation with plaque stabilization.

Ezetimibe inhibits the uptake of biliary and dietary cholesterol into enterocytes, leading to a reduction in serum cholesterol levels.[21] In combination with a statin, ezetimibe synergistically

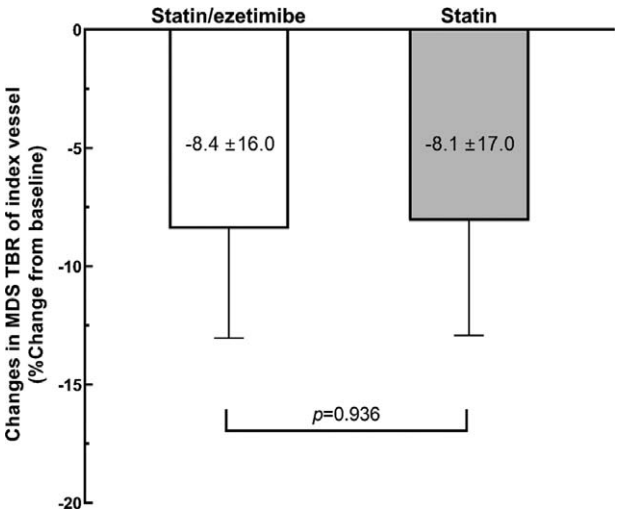


**Figure 2.** Changes of carotid atherosclerotic plaque inflammation after the statin/ezetimibe or statin treatments. The primary outcome (percentage change in MDS TBR) was similar between the statin/ezetimibe and statin groups. MDS = most diseased segment, TBR = target-to-background ratio.

reduces LDL-C levels, and may reverse the atherosclerotic process.[22] Furthermore, the improved reduction of outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) demonstrated that ezetimibe, when added to statin therapy, improves cardiovascular outcomes in patients with acute coronary syndrome.[14] Current guidelines recommend high-intensity or moderate-intensity statin monotherapy based on ASCVD risk, and ezetimibe as a second-line therapy when the target goal is not met with the maximum tolerable dose of statin.[6,7] However, in real-world clinical practice, low-intensity statin/ezetimibe combination therapy is often used instead of high-intensity statin monotherapy due to concerns about statin-related side effects. This approach seems to be an attractive therapeutic option for high-risk patients with ASCVD who are intolerant to high-intensity statin therapy. Unfortunately, there are no outcome studies available to definitively compare the 2 approaches in this clinical setting. The Cholesterol Treatment Trialists' (CTT) collaboration demonstrated that the reduction of cardiovascular events observed with statin therapy was proportional to the magnitude of LDL-C lowering.[1,2] In addition, incremental LDL-C lowering by nonstatins on top of statin therapy can translate into further reductions in cardiovascular events. The cardiovascular benefits of LDL-C lowering therapy seem to be directly related to the amount and duration of LDL-C that is achieved. However, the relative efficacy and safety of statin/ezetimibe combination therapy compared to equivalent statin monotherapy remains uncertain.

Little data are available directly comparing the effects of the 2 treatment strategies on atherosclerotic plaque inflammation, and the available trials are not large enough to resolve ongoing issues.

| Subgroups | Primary endpoint | | 95% CI for the difference | P value | P value for interaction |
|---|---|---|---|---|---|
| | Statin/Ezetimibe | Statin | | | |
| Overall | -8.4 ± 16.0 | -8.1 ± 17.0 | | 0.936 | - |
| Age | | | | | |
| ≥ 65 years | -10.2 ± 14.1 | -8.6 ± 17.6 | | 0.885 | 0.762 |
| < 65 years | -7.3 ± 17.2 | -7.8 ± 17.0 | | 0.539 | |
| Sex | | | | | |
| Male | -9.3 ± 14.6 | -9.5 ± 16.1 | | 0.939 | 0.608 |
| Female | -2.3 ± 24.2 | 2.7 ± 21.3 | | 0.717 | |
| Diagnosis | | | | | |
| NSTE-ACS | -2.8 ± 18.0 | -6.5 ± 13.3 | | 0.546 | 0.489 |
| STEMI | -10.3 ± 15.0 | -8.8 ± 18.5 | | 0.705 | |
| Baseline LDL-C | | | | | |
| ≥ 100mg/dl | -9.6 ± 14.5 | -10.4± 15.2 | | 0.813 | 0.631 |
| < 100mg/dl | -5.9 ± 19.0 | -3.0 ± 20.8 | | 0.705 | |
| Baseline hs-CRP | | | | | |
| ≥ 0.2 | -10.8 ± 13.8 | -11.6 ± 17.1 | | 0.857 | 0.901 |
| < 0.2 | -6.1± 17.8 | -6.1 ± 16.9 | | 0.997 | |
| Baseline TBR | | | | | |
| ≥ 2.0 | -3.9 ± 16.4 | -3.6 ± 18.4 | | 0.938 | 0.939 |
| < 2.0 | -14.2 ± 13.5 | -14.3 ± 12.9 | | 0.974 | |
| Regimen | | | | | |
| R10 vs. S/E10/10 | -10.2 ± 17.5 | -5.8 ± 15.8 | | 0.357 | 0.942 |
| R20 vs. R/E5/10 | -6.2 ± 13.9 | -10.8 ± 17.7 | | 0.329 | |



**Figure 3.** Subgroup analysis of the change in primary outcome. Subgroup analysis of the primary outcome was conducted for the following variables: age, sex, diagnosis, baseline LDL-C, baseline hs-CRP, baseline TBR, and regimens. Subgroup by treatment interactions were tested using this model. There was no heterogeneity between the major subgroups with regards to the primary outcome. hs-CRP = high sensitivity C-reactive protein, LDL-C = low-density lipoprotein cholesterol, NSTE-ACS = non-ST segment elevation myocardial infarction, R/E5/10 = rosuvastatin 5 mg/ezetimibe 10 mg, R10 = rosuvastatin 10 mg, R20 = rosuvastatin 20 mg, S/E 10/10 = simvastatin 10 mg/ezetimibe 10 mg, STEMI = ST-segment elevation myocardial infarction.

A pooled analysis of individual patient data may provide more information about the relative merits of 2 approaches than any individual study.[23] In our pooled analysis, both approaches were equally effective for both primary and secondary endpoints, and their treatment effects mirrored those in both studies individually. There was also no evidence of meaningful heterogeneity in terms of treatment effect for atherosclerotic plaque inflammation in any of the subgroups. These findings suggest that the 2 approaches may be equivalent for prevention of cardiovascular events.

Several limitations of this study should be noted. First, the unmeasured confounders may bias our results. However, the study protocols for 2 trials were the same, and analysis was performed using the same standardized methods. Second, the trials enrolled patients with mild carotid atherosclerosis. Therefore, findings of the present study may not apply to patients with significant carotid artery disease (lumen diameter stenosis >50%). Finally, we used serial $^{18}$FDG PET/CT imaging to compare the efficacy of the 2 therapeutic approaches. Although this is a useful surrogate maker of atherosclerotic plaque inflammation, large-scale outcome trials may be needed to reach a definite conclusion on the comparative effectiveness of the 2 approaches.

## 5. Conclusion

In patients with mild carotid atherosclerosis and acute coronary syndrome, the reduction in carotid atherosclerotic plaque inflammation by statin/ezetimibe combination therapy was equivalent to that by the statin monotherapy.

## Author contributions

**Conceptualization:** Minyoung Oh, Cheol Whan Lee.
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**Supervision:** Dae Hyuk Moon, Cheol Whan Lee.
**Writing – original draft:** Minyoung Oh.
**Writing – review & editing:** Cheol Whan Lee.

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