Effects of ezetimibe/simvastatin 10/10 mg versus Rosuvastatin 10 mg on carotid atherosclerotic plaque inflammation

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Abstract

Background: Using 18F-fluorodeoxyglucose (18FDG) positron emission tomography-computed tomography (PET/CT) imaging, we examined the effects of ezetimibe/simvastatin 10/10 mg versus rosuvastatin 10 mg on carotid atherosclerotic plaque inflammation. Whether the combination therapy of ezetimibe with low-dose statin is as effective as potent statin monotherapy in attenuating carotid atherosclerotic plaque inflammation remains unclear.

Methods: In this 2-by-2 factorial trial, 50 patients with 18FDG uptake (target-to-background ratio [TBR] ≥ 1.6) in the carotid artery and acute coronary syndrome were randomized to receive either simvastatin/ezetimibe 10/10 mg or rosuvastatin 10 mg. 18FDG PET/CT examinations were performed at baseline and at 6 months. The percent change in the TBR of the index vessel at the most diseased segment (MDS) was the primary endpoint.

Results: Baseline characteristics of the two groups were largely similar. At 6-month follow-up, the MDS TBR of the index vessel and aorta significantly decreased in ezetimibe/simvastatin group and tended to decrease in rosuvastatin group. However, the percent change in the MDS TBR of the index vessel was similar between the 2 groups (−10.22 ± 17.49% vs. −5.84 ± 15.78%, respectively, p = 0.357), as was the percent change in the whole vessel TBR of the index vessel. Likewise, the changes in the MDS TBR or whole vessel TBR of the aorta were similar in both groups. Total cholesterol and low-density lipoprotein cholesterol levels improved to a similar degree in both groups.

Conclusion: Treatment with ezetimibe/simvastatin versus rosuvastatin resulted in a similar improvement of carotid atherosclerotic plaque inflammation, suggesting their equivalent anti-inflammatory effects.

Trial registration: The trial is registered at ClinicalTrials.gov: NCT02378064, 3-4-2015. /IRB No. 2015–0194.

Keywords: Ezetimibe, Plaque inflammation, Statin, Positron emission tomography

Background

Statins have been extensively studied in both primary and secondary prevention trials, and statin therapy has been shown to reduce the risk of death and cardiovascular events in a broad range of patient populations [1–3]. There is a linear relationship between the magnitude of low-density lipoprotein (LDL)-cholesterol reduction and the magnitude of cardiovascular risk reduction, indicating that statins exert their beneficial effects primarily by decreasing LDL cholesterol [1, 2, 4]. In addition, the overall benefits of statin therapy seem to exceed that which might be expected from changes in LDL-cholesterol levels alone [5–8]. Statins not only inhibit cholesterol biosynthesis but also the biosynthesis of isoprenoids, which might be implicated in endothelial dysfunction and vascular inflammation [7]. Furthermore, statins lower C-reactive protein levels, which suggests that the efficacy of statins might be partly due to their anti-inflammatory effects [3, 9–11]. In recent years, however, large-scale randomized controlled trials with non-statin cholesterol-lowering therapies have shown similar benefits to statins in reducing the risk of cardiovascular events [12, 13], thereby raising questions about...
potentially unique pleiotropic properties of statins. Indeed, it is unclear whether statins have effects other than those that lower LDL cholesterol that may suppress atherosclerotic plaque inflammation.

Statins side effects are related to the dose or potency of the given drugs [14, 15], and a combination therapy of ezetimibe with low-dose statin is occasionally used to minimize adverse effects. However, there is little information about whether this approach is as effective as potent statin monotherapy in decreasing LDL cholesterol levels and attenuating atherosclerotic plaque inflammation. Using 18F-fluorodeoxyglucose (18FDG) positron emission tomography (PET) imaging, we examined the effects of ezetimibe/simvastatin 10/10 mg versus rosvastatin 10 mg on carotid atherosclerotic plaque inflammation in patients with acute coronary syndrome.

Methods
Between May 2015 and December 2017, we conducted a single center, randomized, open label trial using a 2-by-2 factorial design (ClinicalTrials.gov number, NCT02378064). The trial evaluated cholesterol-lowering therapy with ezetimibe/simvastatin 10/10 mg versus rosuvastatin 10 mg and blood pressure-lowering therapy with fimasartan versus amlodipine in patients with acute coronary syndrome. The results of the blood pressure-lowering therapy have been previously reported in another study, in which detailed in-inflammation in patients with acute coronary syndrome. Between May 2015 and December 2017, we conducted a single center, randomized, open label trial using a 2-by-2 factorial design (ClinicalTrials.gov number, NCT02378064). The trial evaluated cholesterol-lowering therapy with ezetimibe/simvastatin 10/10 mg versus rosuvastatin 10 mg and blood pressure-lowering therapy with fimasartan versus amlodipine in patients with acute coronary syndrome. The results of the blood pressure-lowering therapy have been previously reported in another study, in which detailed in-inflammation in patients with acute coronary syndrome. Between May 2015 and December 2017, we conducted a single center, randomized, open label trial using a 2-by-2 factorial design (ClinicalTrials.gov number, NCT02378064). The trial evaluated cholesterol-lowering therapy with ezetimibe/simvastatin 10/10 mg versus rosuvastatin 10 mg and blood pressure-lowering therapy with fimasartan versus amlodipine in patients with acute coronary syndrome. The results of the blood pressure-lowering therapy have been previously reported in another study, in which detailed in-inflammation in patients with acute coronary syndrome. Between May 2015 and December 2017, we conducted a single center, randomized, open label trial using a 2-by-2 factorial design (ClinicalTrials.gov number, NCT02378064). The trial evaluated cholesterol-lowering therapy with ezetimibe/simvastatin 10/10 mg versus rosuvastatin 10 mg and blood pressure-lowering therapy with fimasartan versus amlodipine in patients with acute coronary syndrome. The results of the blood pressure-lowering therapy have been previously reported in another study, in which detailed in
the one of the carotid arteries with the highest $^{18}$FDG activity was chosen as the index vessel at baseline [18].

The percent change in the MDS TBR of the index vessel calculated as \((MDS \ TBR \ at \ 6 \ months \ - \ MDS \ TBR \ at \ baseline) / (MDS \ TBR \ at \ baseline) \times 100\) was defined as the primary endpoint. Secondary endpoints were changes in lipid profiles [total cholesterol, triglyceride, high-density lipoprotein (HDL) cholesterol, and LDL cholesterol], systolic/diastolic blood pressure, and highsensitivity C-reactive protein.

A sample of 22 participants per treatment group was estimated to provide the 90% power to detect a 15% difference in the primary endpoint between the rosuvastatin and ezetimibe/simvastatin groups (assuming a SD of 15% in each group) with a significance level of 0.05, using a two-sided test. With an anticipated dropout rate of 10%, total 50 patients (25 patients in each group) was necessary to provide an adequate number of evaluable patients. Categorical variables were expressed as frequencies, whereas continuous variables as means ± standard deviations or medians with interquartile ranges. The paired \(t\)-test or Wilcoxon rank sum test were used to compare the changes of continuous variables in each group, and the unpaired \(t\)-test or Mann-Whitney U-test for differences between groups. An analysis with two-sided \(p\)-value < 0.05 was considered statistically significant.

### Results

Among the 146 screened patients with acute coronary syndrome, 96 did not fulfill the eligibility criteria for the present study, and 50 patients were eventually randomized to either the ezetimibe/simvastatin group or the rosuvastatin group. Exclusion was due to poor left ventricular function \((n = 6)\), the absence of carotid

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**Table 1** Baseline Clinical characteristics

| Characteristics                  | Ezetimibe/simvastatin \((n = 25)\) | Rosuvastatin \((n = 25)\) | \(p\)-value |
|----------------------------------|------------------------------------|---------------------------|-------------|
| Age, years                       | 62.5 ± 7.4                         | 59.2 ± 8.8                | 0.154       |
| Men                              | 22 (88.0%)                         | 21 (84.0%)                | 0.684       |
| Current smoker                   | 4 (16.0%)                          | 5 (20.0%)                 | 0.713       |
| Diabetes mellitus                | 2 (8.0%)                           | 3 (12.0%)                 | 0.637       |
| Hypertension                     | 17 (68.0%)                         | 10 (40.0%)                | 0.047       |
| Diagnosis                        |                                    |                           | 0.301       |
| STEMI                            | 19 (76.0%)                         | 19 (76.0%)                |             |
| NSTE-ACS                         | 6 (2.0%)                           | 6 (24.0%)                 |             |
| Culprit artery of ACS            |                                    |                           | 0.345       |
| Left anterior descending coronary| 17 (68.0%)                         | 16 (64.0%)                |             |
| Left circumflex coronary         | 2 (8.0%)                           | 0 (0%)                    |             |
| Right coronary                   | 6 (24.0%)                          | 8 (32.0%)                 |             |
| Ramus intermedium                | 0 (0%)                             | 1 (40%)                   |             |
| Culprit lesion PCI               | 24 (97.5%)                         | 25 (100%)                 | 0.848       |
| Left ventricular ejection fraction (%) | 52.9 ± 8.2                       | 53.9 ± 7.3                | 0.718       |
| Medications at the time of follow-up |                                   |                           |             |
| Aspirin                          | 25 (100%)                          | 25 (100%)                 | 1.0         |
| P2Y12 inhibitors                 | 25 (100.0%)                        | 25 (100.0%)               | 1.0         |
| \(\beta\)-blockers               | 22 (88.0%)                         | 19 (76.0%)                | 0.269       |
| Angiotensin II receptor blocker   | 12 (48.0%)                         | 13 (52.0%)                | 0.777       |
| Calcium channel blocker          | 13 (52.0%)                         | 12 (48.0%)                | 0.777       |

**CAD** Coronary artery disease, **STEMI** ST-Segment elevation myocardial infarction, **NSTE-ACS** Non-ST-segment elevation-acute coronary syndrome, **PCI** Percutaneous coronary intervention
atherosclerosis \((n = 85)\), and patient refusal \((n = 5)\) (Fig. 1). Six-month follow-up PET/CT examination was performed in all patients.

The baseline characteristics were largely similar between the two groups (Table 1). The mean age of the patients was 60.9 ± 8.2 years, the mean systolic blood pressure was 145.5 ± 14.21 mmHg, and the mean LDL cholesterol level was 118.9 ± 34.52 mg/dL (Table 2). Men comprised 86% of the patients. Clinical presentations were non-ST-segment elevation acute coronary syndrome in 24.0% of the patients, and ST-segment elevation myocardial infarction in 76.0% of the patients and. Percutaneous coronary intervention was performed in most patients (98.0%), except one patient (2.0%) with medications.

Lipid profiles, blood pressure, and high-sensitivity C-reactive protein levels at baseline were similar between the 2 groups (Table 2). Total cholesterol and LDL cholesterol levels significantly decreased in both groups at 6-month follow-up \((p < 0.001)\). High sensitivity C-reactive protein levels significantly decreased in the rosuvastatin group \((p = 0.016)\) and tended to decrease in the ezetimibe/simvastatin group \((p = 0.090)\). However, HDL cholesterol and triglyceride levels did not significantly change in either group. Likewise, blood pressure changes were not different between the 2 groups (systolic: 17.7 ± 13.38% for the rosuvastatin group vs. 15.8 ± 15.72% for the ezetimibe/simvastatin group; \(p = 0.650\); diastolic: 15.8 ± 17.18% vs. 12.3 ± 17.39%, respectively; \(p = 0.481\)).

Figure 2 shows representative images of improved \(^{18}\)FDG uptake in the carotid plaque after ezetimibe/simvastatin therapy. As summarized in Table 3, baseline \(^{18}\)FDG PET/CT parameters were similar between the 2 groups. The MDS TBR of the index vessel at 6-month follow-up significantly decreased in the ezetimibe/simvastatin groups \((p = 0.002)\) and tended to decrease in the rosuvastatin group \((p = 0.077)\). However, the percent change in the MDS TBR of the index vessel (primary endpoint) was not significantly different between both groups \((-10.22 ± 17.49\%\) vs. -5.84 ± 15.78\%, respectively, \(p = 0.357\) (Fig. 3). Similarly, the MDS TBR of the ascending aorta significantly decreased in the ezetimibe/simvastatin groups \((p = 0.002)\) and tended to decrease in the rosuvastatin group \((p = 0.052)\). The percent change in the whole vessel TBR of the index vessel did not differ between the 2 groups. Similar results were detected for changes in the MDS TBR and whole vessel TBR of the aorta. No significant correlations were found between changes in the lipid profile, C-reactive protein levels, or

### Table 2 Laboratory Findings

| Characteristics     | Ezetimibe/simvastatin \((n = 25)\) | Rosuvastatin \((n = 25)\) | \(p\)-value |
|---------------------|-----------------------------------|---------------------------|-------------|
| Total cholesterol (mg/dl) |                                   |                           |             |
| Baseline            | 174.2 ± 38.90                     | 178.2 ± 31.80             | 0.689       |
| 6 months            | 135.6 ± 23.65                     | 129.4 ± 23.37             | 0.359       |
| Triglyceride (mg/dl) |                                   |                           |             |
| Baseline            | 110.7 ± 46.88                     | 115.0 ± 56.11             | 0.771       |
| 6 months            | 113.8 ± 43.70                     | 115.2 ± 44.93             | 0.914       |
| LDL cholesterol (mg/dl) |                                  |                           |             |
| Baseline            | 114.3 ± 34.83                     | 123.5 ± 34.29             | 0.349       |
| 6 months            | 87.3 ± 20.00                      | 81.1 ± 21.9               | 0.301       |
| HDL cholesterol (mg/dl) |                                |                           |             |
| Baseline            | 45.5 ± 8.93                       | 45.7 ± 10.06              | 0.941       |
| 6 months            | 45.2 ± 7.95                       | 46.7 ± 8.32               | 0.490       |
| Hs-CRP (mg/L)       | 0.34 ± 0.68                       | 0.38 ± 0.43               | 0.801       |
| 6 months            | 0.10 ± 0.17                       | 0.11 ± 0.24               | 0.886       |

*Hs-CRP* High sensitivity C-reactive protein
blood pressure and percent changes in the MDS TBR of the index vessel.

**DISCUSSION**

In this study, we found that in patients with carotid artery disease and acute coronary syndrome, both ezetimibe/simvastatin 10/10 mg and rosuvastatin 10 mg improved carotid atherosclerotic plaque inflammation without between-group differences. Aortic inflammation was also similarly decreased in both groups. Likewise, changes in the serum levels of total cholesterol, LDL cholesterol, and high-sensitivity C-reactive protein were not different in both groups. These findings suggest that treatment with ezetimibe plus low-dose statin versus potent statin monotherapy offers comparable anti-inflammatory effects when administered at equivalent daily doses.

Statins remains the medicine of choice for cardiovascular risk reduction. For patients with clinical atherosclerotic cardiovascular disease or diabetes mellitus, moderate- or high-intensity statin therapy is primarily recommended [19]. In real-word practice, however, an ezetimibe plus low-intensity statin regimen is occasionally prescribed to treat these patients owing to concerns about the side effects of statins. The benefits observed with statin therapy may not be attributed entirely to their cholesterol-lowering properties but also to pleiotropic effects. However, it is unclear whether the combination therapy of ezetimibe with low-intensity statin has similar pleiotropic effects compared with potent statin monotherapy to yield the same degree of LDL cholesterol reduction. Previously, simvastatin/ezetimibe 10/10 mg and rosuvastatin 10 mg at equivalent LDL cholesterol-lowering doses were shown to similarly reduce plasma markers of oxidative stress and inflammation activity [20]. In the present study, there was no difference between the 2 regimens in reducing carotid atherosclerotic plaque inflammation, suggesting equivalent anti-inflammatory effects. These findings support the current clinical practice of reducing LDL cholesterol using a combination of ezetimibe plus low-intensity statin.

Ezetimibe selectively blocks intestinal absorption of dietary and biliary cholesterol and promotes a compensatory increase in cholesterol synthesis [21]. As a result, ezetimibe leads to a substantial additional reduction in LDL cholesterol levels when added to statin therapy [22]. However, the question of whether ezetimibe shares similar anti-atherosclerotic properties with statins has been debated [23]. In the Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression (ENHANCE) trial [24], combination therapy with ezetimibe/simvastatin did not show a significant difference in intima-media thickness versus the use of simvastatin alone. In contrast, ezetimibe/fluvastatin combination therapy was found to increase the fibrous cap thickness of lipid-rich plaque, as compared to fluvastatin monotherapy [25]. In the PRECISE-IVUS study, ezetimibe/atorvastatin resulted in a more remarkable reduction of LDL cholesterol compared to atorvastatin monotherapy, with favorable effects on coronary atherosclerotic plaque [26]. Furthermore, the combination of ezetimibe and simvastatin versus simvastatin monotherapy resulted in the incremental lowering of LDL cholesterol levels and improved cardiovascular outcomes [12]. Overall, an ezetimibe plus low-intensity statin or potent statin alone at equivalent LDL cholesterol-lowering doses appears to have comparable anti-atherosclerotic effects. These

| Characteristics | Ezetimibe / simvastatin (n = 25) | Rosuvastatin (n = 25) | p-value between groups |
|-----------------|-------------------------------|----------------------|------------------------|
| MDS TBR of index carotid artery | Baseline 2.37 ± 0.46 2.23 ± 0.41 0.271 | Follow-up 2.07 ± 0.29 2.09 ± 0.46 0.889 | Nominal change −0.30 ± 0.43 −0.15 ± 0.40 0.197 |
| | p-value compared with baseline 0.002 0.077 | Percent change (primary endpoint) −10.22 ± 17.49 −5.84 ± 15.78 0.357 | Whole vessel TBR of index carotid artery |
| | Baseline 2.00 ± 0.39 1.94 ± 0.31 0.537 | Follow-up 1.81 ± 0.26 1.83 ± 0.35 0.772 | Nominal change −0.19 ± 0.38 −0.11 ± 0.38 0.419 |
| | p-value compared with baseline 0.017 0.168 | Percent change −6.81 ± 19.06 −3.95 ± 17.01 0.579 | MDS TBR of aorta |
| | Baseline 2.58 ± 0.45 2.57 ± 0.45 0.912 | Follow-up 2.27 ± 0.34 2.35 ± 0.46 0.459 | Nominal change −0.31 ± 0.44 −0.21 ± 0.52 0.466 |
| | p-value compared with baseline 0.002 0.052 | Percent change −10.35 ± 16.24 −6.80 ± 18.36 0.473 | Whole vessel TBR of aorta |
| | Baseline 2.47 ± 0.43 2.47 ± 0.45 0.959 | Follow-up 2.19 ± 0.33 2.26 ± 0.45 0.507 | Nominal change −0.29 ± 0.43 −0.20 ± 0.52 0.549 |
| | p-value compared with baseline 0.003 0.063 | Percent change −9.580 ± 16.45 −6.58 ± 19.04 0.526 | Nominal change is calculated as follow-up minus baseline, and percent change as (follow-up minus baseline)/baseline×100. MDS Most diseased segment, TBR Tissue blood ratio. |
findings are also compatible with previous studies showing that the clinical benefit of cholesterol lowering therapies mostly depends on the absolute reduction in LDL cholesterol and the total duration of therapy [27, 28].

Several potential limitations of the study need to be addressed. First, the number of study subjects was relatively small, which may not have allowed for sufficient power to detect a subtle difference in the MDS TBR of the index vessel. Second, an open-label design is subject to inherent limitations. We tried to overcome the limitations by using blind 18FDG PET/CT evaluations. Third, a placebo arm was not included owing to ethical considerations. Finally, the results of the paper are not generalizable to all patients with acute coronary syndrome or at high risk for cardiovascular events, but to those who cannot tolerate at least moderate-intensity statin therapy.

**Conclusion**

In this study, we found that both ezetimibe/simvastatin 10/10 mg and rosuvastatin 10 mg resulted in a similar improvement of carotid atherosclerotic plaque inflammation in patients with carotid artery disease and acute coronary syndrome. It suggests that their anti-inflammatory effects are equivalent.

**Abbreviations**

18FDG: 18F-fluorodeoxyglucose; CT: Computed tomography; HDL: High density lipoprotein; LDL: Low-density lipoprotein; MDS: Most diseased segment; PET: Positron emission tomography; ROI: Region-of-interest; SUVs: Standardized uptake values; TBR: Target to background ratio

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**Authors’ contributions**

MO and CWL were involved in conception and design of the study. MO, HK, EWS, CS, & D-HK were involved in collection and analysis of the data. DHM provided scientific supervision. All authors reviewed and approved the final manuscript. CWL was the principal investigator.

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**Availability of data and materials**

The datasets generated and analysed during the current study are not publicly available due to patient confidentiality but are available from the corresponding author on reasonable request.

**Ethics approval and consent to participate**

The Institutional Review Board at Asan Medical Center approved this study (No. 2015–0194). All patients provided written informed consent prior to enrollment in accordance with the 1975 Declaration of Helsinki.

**Consent for publication**

Not applicable.
Competing interests
The authors declare that they have no conflicts of interest.

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