

## Editorial



# Effects of Combination Therapy of Statin and Thiazolidinedione on Vascular Inflammation

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The authors have no financial conflicts of  
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Thiazolidinediones (TZDs) are anti-diabetic agents that lower plasma glucose levels by increasing insulin sensitivity in peripheral tissues. As a selective ligand of peroxisome proliferator-activated receptor (PPAR)- $\gamma$ , TZDs also exert beneficial effects on lipid metabolism and inflammatory processes.<sup>1)</sup> Current studies have shown that TZDs are effective in reducing inflammatory markers<sup>2)</sup> and attenuates the progression of atherosclerosis.<sup>3)</sup> Also, they can exert direct influence on endothelial cell, vascular smooth muscle cell, and macrophage.<sup>4)</sup> Statins, 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors, are one of the most widely used medications in clinical practice. In addition to the benefit of statin in lowering the low-density lipoprotein (LDL) cholesterol, they act as anti-inflammatory agents through pleiotropic effects<sup>5)</sup> and randomized clinical trials have demonstrated their benefits in the primary and secondary prevention of coronary heart disease.<sup>6,7)</sup>

In the current issue of the *Korean Circulation Journal*,<sup>8)</sup> the authors evaluated the effect of the addition of pioglitazone (30 mg/day) on atherosclerotic inflammation in patients taking atorvastatin (20 mg/day). This study enrolled 33 statin-naïve patients with stable coronary artery disease (CAD) and carotid plaque  $\geq 3$  mm and subjects were randomized into atorvastatin (n=16) and atorvastatin plus pioglitazone (n=17) for 3 months. Serial <sup>18</sup>F-fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT) was used to evaluate the arterial inflammation before and after treatment by measuring the arterial target-to-background ratio (TBR) of the index vessel. After 3 months of treatment, a significant reduction in the TBR was observed in both groups, but the difference between the 2 groups showed marginal statistical significance ( $-0.06$  in atorvastatin group and  $-0.10$  in atorvastatin plus pioglitazone group;  $p=0.058$ ). So, the authors classified the patients according to the baseline TBR value, and found that addition of pioglitazone was more effective in patients whose baseline TBR value was above the median ( $-0.03$  in atorvastatin group and  $-0.14$  in atorvastatin plus pioglitazone group;  $p<0.001$ ).

There are several studies investigating the effect of combining statin with TZD. Hanefeld et al.<sup>2)</sup> investigated the anti-inflammatory effect of simvastatin or pioglitazone monotherapy or simvastatin plus pioglitazone group in non-diabetic subjects with cardiovascular disease (CVD). After 3 months of treatment, simvastatin plus pioglitazone group had an additive

effect in reducing C-reactive protein (CRP) and matrix metalloproteinase-9 (MMP-9). Plasminogen activator inhibitor (PAI)-1 or homeostasis model assessment (HOMA) were improved in pioglitazone group only.<sup>2)</sup> Lazich et al.<sup>9)</sup> also demonstrated that simvastatin/rosiglitazone combination had a greater reduction in CRP and increase in adiponectin compared to simvastatin monotherapy group in patients with metabolic syndrome.

The overall results of current study are in line with previous studies. However, unlike previous studies using the serum markers as an indicator of vascular inflammation, this study used FDG-PET/CT. FDG accumulation in atherosclerotic plaque is significantly higher in plaque at risk of rupture, and is known to predict restenosis after revascularization or mortality.<sup>10)</sup> So, FDG-PET/CT is useful in recognizing potential vulnerable plaque and may have a more clinical significance. Another difference is the characteristics of study participants. Previous studies enrolled subjects with CVD or metabolic syndrome, but they did not have diabetes. The current study included 22 (67%) diabetes or impaired fasting glucose, and extended the additive anti-inflammatory effect of pioglitazone to subjects with abnormal glucose tolerance.

In conclusion, despite the limitation that the overall absolute reduction in TBR after the addition of pioglitazone was too small as it is 0.04 or about 0.04 which is too small, this study demonstrated a potential role of the addition of pioglitazone in patients with sustained vessel inflammation after statin therapy. Further studies in larger scale subjects with various characteristics are warranted.

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