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EDITORIAL COMMENT

The Complexity of Physiology in the Evaluation of the Effect of Medication for Cardiovascular Disease*

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The beneficial effects of statins in the treatment of atherosclerotic cardiovascular diseases are supported by a wealth of evidence.[1,2] The stabilization and prevention of the progression of atherosclerosis, proven by several imaging studies, is thought to be one of the mechanisms of the favorable effect of statins on patient outcome.[3,4]

From intuitive prediction, the decreased plaque burden leads to a reduction of resistance from plaque, thereby increasing the value of fractional flow reserve (FFR). However, the beneficial effects of statins on the value of FFR are scarcely reported.

In this issue of *JACC: Asia*, Lee et al[5] report a comprehensive analysis of the effects of statins on coronary physiology and anatomy. They collected data on FFR, coronary flow reserve (CFR), index of microcirculatory resistance (IMR), and intravascular ultrasound during the index procedure and 12-month follow-up from 95 patients who received statin therapy.

Intensive lipid-lowering therapy led to the significant decrease in low-density lipoprotein cholesterol (LDL-C) from 119.9 to 80.1 mg/dL ($P < 0.001$), concomitant with the significant reduction of atheroma volume from 9.52 to 9.00 mm^2 ($P < 0.001$). However, they did not observe a significant change in the FFR value (0.88 at baseline and 0.87 at the 12-month follow-up; $P = 0.694$). Further analysis showed a significant improvement of the FFR value from 0.87 ± 0.06 to 0.89 ± 0.07 ($P = 0.014$) in patients with optimally modified LDL-C (LDL-C level of 70 mg/dL or ≥50% reduction from the baseline). These patients also showed a larger reduction in atheroma volume than the general population (-6.8% vs -5.5%). However, the percent change in FFR was considerably smaller than that in atheroma volume (2.3% vs -6.8%). This finding is surprising considering the strong relationship between coronary events and FFR values[6] and the degree of decreased cardiac events attributable to intensive lipid-lowering therapy.[1,2]

One possible explanation for this observation is that the enlargement of the lumen area may occur after the regression of plaque and vessel area in a method opposite to that of atherosclerosis progression. It is well known that the vessel area enlarges at the beginning of the atherosclerotic process to maintain the lumen area to maintain coronary flow.[7] In this study, the lumen area remained unchanged (3.84 vs 3.70 mm^2; $P = 0.669$), even in patients with optimally modified LDL-C. Although it has been reported that the presence of positive remolding can also negatively influence the FFR value,[8] the magnitude of the effect may be negligible when compared to the change in lumen area. It may take a longer time to observe robust changes in the lumen area and FFR values after medical therapy.

Another possible explanation is that statins may improve microvascular function. Although not significant, the improvement of CFR (4.25 vs 4.69; $P = 0.427$) and IMR (16.33 vs 15.91; $P = 0.809$) values was observed in patients with optimally modified LDL-C.

FFR does not directly measure coronary flow but assumes that there is a linear relationship between coronary pressure and coronary flow under the condition of maximum hyperemia.[9] FFR is defined as the ratio of hyperemic coronary flow in the presence of

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epicardial coronary stenosis to the normal hyperemic maximum flow.[10] However, it is known that FFR may underestimate lesion severity in the presence of microvascular dysfunction, which can decrease hyperemic coronary flow.[11,12] The impaired vasodilatation in response to vasodilatory drugs decreases the hyperemic coronary flow, resulting in a decrease in the pressure gradient caused by stenotic coronary lesions, thus preventing the FFR value from decreasing.[13] If statins improve the vasodilatory function of the microvasculature and at the same time decrease the atheroma volume, some of the decreased resistance caused by a reduction in the atheroma volume may be reversed with the increased coronary flow.

Further studies with a larger cohort of patients and longer follow-up period are warranted to corroborate the relationship between intensive lipid-lowering therapy and FFR, CFR, IMR values and anatomic parameters.

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