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Statins in Variant Angina

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REFER TO THE PAGE 58-63

Variant angina pectoris (VAP) is a form of angina pectoris that shows transient ST-segment elevation on electrocardiogram during an attack of chest pain and is caused by coronary artery spasm.[1)2)] Although the pathogenesis of coronary artery spasm has not been fully elucidated, endothelial dysfunction and enhanced vascular smooth muscle contractility play major roles in the pathogenesis of coronary artery spasm. Other contributing factors of coronary artery spasm include increased oxidative stress, inflammation, magnesium deficiency, genetic susceptibility, and imbalance in autonomic nervous activity.[1-3)]

Statins have been demonstrated to significantly improve the prognosis and outcome of patients with atherosclerosis mainly because statins can lower low density lipoprotein (LDL)-cholesterol concentration.[4)5)] However, recent studies suggested that statins may affect the cardiovascular system beyond their effect on the lipid profile (called pleiotropic effects).[6)] Pleiotropic effects of statins include improvement of endothelial dysfunction, increased nitric oxide bioavailability, antioxidant properties, inhibition of inflammatory responses, and stabilization of atherosclerotic plaques, which may provide a cardiovascular benefit beyond that expected from LDL-cholesterol lowering alone.[7)8)] These effects of modulated endothelial function and reduced inflammatory processes have been pointed out as one of the possible mechanisms of reducing coronary artery vasospasm in VAP.[8)] Recent clinical evidences also showed that combined therapy with a statin and a calcium channel blocker may attenuate coronary vasoconstriction as well as systemic endothelial dysfunction in patients with VAP.[9)10)] In this issue of *Journal of Cardiovascular Ultrasound*, Kim et al.[11)] also support the evidence that the use of atorvastatin, regardless of dosage, could improve systemic endothelial function as measured by flow mediated dilation of the brachial artery in patients with VAP. Collectively, statin might modify the underlying pathogenesis of coronary artery spasm and be a novel therapeutic drug for coronary artery spasm in patients with VAP.

Kim et al.[11)] also hypothesized that atorvastatin 40 mg could improve more endothelial function and carotid intima media thickness than those of atorvastatin 10 mg. It has not been demonstrated the dose-dependent effects of statin therapy on vascular function in patients with VAP. Experimental studies support this hypothesis that statins can dose-dependently increase the production of nitric oxide by activation of endothelial nitric oxide synthase and increasing its mRNA half-life, independent of cholesterol levels.[12)13)] Clinical evidence also suggested that intensive lipid-lowering therapy with statin provides significant clinical benefit beyond lipid-lowering therapy in patients with atherosclerosis, which is suggestive of dose-dependent pleiotropic effects of statin.[14)]

However, Kim et al.[11)] in this issue of *J Cardiovasc Ultrasound* concluded that the use of high dose statin (atorvastatin 40 mg) did not show significant additional benefit as compared with the use of low dose statin (atorvastatin 10 mg) with regarding carotid intima media thickness and endothelial function. I have some comments about this study. First, atorvastatin 80 mg as a high dose group rather than atorvastatin 40 mg would be a proper dosage for proving additive beneficial effects of endothelial dysfunction and carotid intima media thickness because no clear evidence exists to support additional beneficial effects of medium-dose statin (atorvastatin 40 mg) on vascular function as well as clinical benefits. Second, the study duration is relatively shorter (6 month) for the detection of changes of carotid intima media thickness and flow mediated dilation. These changes of both flow mediated dilation and carotid intima media thickness with statins correlated with the duration × treatment intensity product.[15)] It needs more than 2 years for the changes of carotid intima media thickness on the progression of carotid atherosclerosis. Finally, the numbers of the study subjects are relatively small to detect the difference of vascular function between atorvastatin 40 mg and atorvastatin 10 mg. In the study of Kim et al.,[11)] it seems to be more increase of flow mediated dilation in atorvastatin 40 mg group (7.9 ± 2.7% to 9.5 ± 2.8%) than those in atorvastatin 10 mg group (7.7 ± 2.5% to 8.9 ± 2.2%). But, these results were

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statistically insignificant due to under-powered sample size.

Despite some limitations, the present study of Kim et al.[11] showed that an addition of statin to the conventional calcium channel blocker and nitrate for 6 months significantly reduced systemic endothelial dysfunction measured by flow mediated dilation in patient with VAP. Statin might be a promising drug for the treatment of VAP.

References

1. Stern S, Bayes de Luna A. *Coronary artery spasm: a 2009 update. Circulation 2009;119:2531-4.*
2. Kusama Y, Kodani E, Nakagomi A, Otsuka T, Atarashi H, Kishida H, Mizuno K. *Variant angina and coronary artery spasm: the clinical spectrum, pathophysiology, and management. J Nippon Med Sch 2011; 78:4-12.*
3. Yoo SY, Kim JY. *Recent insights into the mechanisms of vasospastic angina. Korean Circ J 2009;39:505-11.*
4. 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;285:2486-97.*
5. Baigent C, Keech A, Kearney PM, Blackwell L, Buck G, Pollicino C, Kirby A, Sourjina T, Peto R, Collins R, Simes R; Cholesterol Treatment Trialists' (CTT) Collaborators. *Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. Lancet 2005;366:1267-78.*
6. Treasure CB, Klein JL, Weintraub WS, Talley JD, Stillabower ME, Kosinski AS, Zhang J, Boccuzzi SJ, Cedarholm JC, Alexander RW. *Beneficial effects of cholesterol-lowering therapy on the coronary endothelium in patients with coronary artery disease. N Engl J Med 1995;332:481-7.*
7. Davignon J, Ganz P. *Role of endothelial dysfunction in atherosclerosis. Circulation 2004;109(23 Suppl 1):III27-32.*
8. Blum A, Shamburek R. *The pleiotropic effects of statins on endothelial function, vascular inflammation, immunomodulation and thrombogenesis. Atherosclerosis 2009;203:325-30.*
9. Tani S, Nagao K, Anazawa T, Kawamata H, Furuya S, Takahashi H, Iida K, Fuji T, Matsumoto M, Kumabe T, Sato Y, Hirayama A. *Treatment of coronary spastic angina with a statin in addition to a calcium channel blocker: a pilot study. J Cardiovasc Pharmacol 2008;52:28-34.*
10. Yasue H, Mizuno Y, Harada E, Itoh T, Nakagawa H, Nakayama M, Ogawa H, Tayama S, Honda T, Hokimoto S, Ohshima S, Hokamura Y, Kugiyama K, Horie M, Yoshimura M, Harada M, Uemura S, Saito Y; SCAST (Statin and Coronary Artery Spasm Trial) Investigators. *Effects of a 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor, fluvastatin, on coronary spasm after withdrawal of calcium-channel blockers. J Am Coll Cardiol 2008;51:1742-8.*
11. Kim KH, Cho SH, Yim YR, Lee KJ, Yum JH, Yoon HJ, Yoon NS, Hong YJ, Park HW, Kim JH, Ahn Y, Jeong MH, Cho JG, Park JC. *Effects of low dose versus high dose statin therapy on the changes of endothelial function and carotid intima-media thickness in patients with variant angina. J Cardiovasc Ultrasound 2013;21:58-63.*
12. Hernández-Perera O, Pérez-Sala D, Navarro-Antolín J, Sánchez-Pascuala R, Hernández G, Díaz C, Lamas S. *Effects of the 3-hydroxy-3-methylglutaryl-CoA reductase inhibitors, atorvastatin and simvastatin, on the expression of endothelin-1 and endothelial nitric oxide synthase in vascular endothelial cells. J Clin Invest 1998;101:2711-9.*
13. Laufs U, La Fata V, Plutzky J, Liao JK. *Upregulation of endothelial nitric oxide synthase by HMG CoA reductase inhibitors. Circulation 1998; 97:1129-35.*
14. van der Harst P, Wagenaar LJ, Buikema H, Voors AA, Plokker HW, Morshuis WJ, Six AJ, Boonstra PW, Nickenig G, Wassmann S, van Veldhuisen DJ, van Gilst WH. *Effect of intensive versus moderate lipid lowering on endothelial function and vascular responsiveness to angiotensin II in stable coronary artery disease. Am J Cardiol 2005;96: 1361-4.*
15. Masoura C, Pitsavos C, Aznaouridis K, Skoumas I, Vlachopoulos C, Stefanadis C. *Arterial endothelial function and wall thickness in familial hypercholesterolemia and familial combined hyperlipidemia and the effect of statins. A systematic review and meta-analysis. Atherosclerosis 2011;214: 129-38.*