

Legacy Effect of Statin Should Not Be Discontinued

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Primarily through lowering low-density lipoprotein cholesterol (LDL-C), statins have an established role in reducing the incidence of stroke and cardiovascular events, and expert consensus guidelines endorse intensive LDL-lowering therapy for secondary prevention of stroke.¹ However, discontinuation of statin is not infrequently encountered in real-world practice for various reasons. Possible reasons include a prior stroke that was a non-atherosclerotic type (i.e., hemorrhagic stroke or cardioembolic stroke), inability of the patient to afford the medications, or drug adverse effects that caused the patient to be instructed by their physician to stop the statin.² Indeed, another stroke registry study showed that discontinuation of statin within the first year after the index event was prompted by the physician rather than by the patient in the majority of cases.³

Discontinuation of statin is found to result in various biochemical and molecular changes within the vascular environment. In the vascular smooth muscle cells increased proatherogenic and procoagulant activity are observed.⁴ Specifically, acute withdrawal of statin is associated with increased expression of tissue factor and monocyte chemoattractant protein-1, and with upregulation of angiotensin II type 1 receptor in the smooth muscle cells.^{4,5} In the vascular endothelium, there are

remarkable reductions of endothelial nitric oxide synthase activity, followed by decreased nitric oxide levels.⁵ These biochemical changes in the endothelium are mediated by increased guanosine triphosphatase (GTPase) activity due to activated GTP-binding protein Rho, which is bound to the increased isoprenoid compounds (the intermediates of the cholesterol biosynthetic pathway) after statin withdrawal.⁵ In a recent meta-analysis, statin therapy showed a beneficial effect on arterial stiffness, which is an independent predictor of cardiovascular events.⁶ Another study comprising 16 healthy volunteers showed that acute withdrawal of statins led to decreased evoked hemodynamic responses reflecting reduced nitric oxide bioavailability.⁷

It is well-known that carotid bifurcation is vulnerable to the accumulation of plaques and thereby lose its elasticity earlier than other vessels. Given that decreased carotid artery distensibility (i.e., increased stiffness and decreased elasticity) is associated with incident ischemic stroke as well as severity of atherosclerosis,⁸ we can deduce that acute withdrawal of statin may increase stiffness in the carotid artery, possibly having a deleterious effect on recurrent vascular events in high cardiovascular risk patients.

To reiterate the importance of maintaining statin medication, Kim et al.⁹ set out to assess the changes in carotid

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artery distensibility after statin withdrawal in 37 dyslipidemia patients free of cerebrovascular diseases by calculating strain and β -stiffness indices based on the mean diameters of common carotid artery during three cardiac cycles. Despite being a relatively small sample size, a transient decrease in carotid artery distensibility was consistent through all the patients at least till 7 days after the discontinuation of statin. This transient decrease in vascular elasticity after statin withdrawal may partly contribute to the worse clinical course in the acute ischemic stroke.

It is not clear whether abrupt statin withdrawal may influence the risk of clinical cardiovascular events, especially among vascular disease-free but high-risk patients. Nevertheless, this study⁹ implies the beneficial legacy effect of statins and endorses early prescription of statins (as such for antiplatelet drugs) at least to preserve the hemodynamic effect in patients with acute stroke setting.

REFERENCES

1. Stone NJ, Robinson JG, Lichtenstein AH, Bairey Merz CN, Blum CB, Eckel RH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2014;129(25 Suppl 2):S1-S45.
2. Park JH, Ovbiagele B. Stroke: LDL and stroke risk clinical practice or target practice? *Nat Rev Neurol*. 2015;11:8-9.
3. Bushnell CD, Olson DM, Zhao X, Pan W, Zimmer LO, Goldstein LB, et al. Secondary preventive medication persistence and adherence 1 year after stroke. *Neurology*. 2011;77:1182-1190.
4. Brandes RP, Beer S, Ha T, Busse R. Withdrawal of cerivastatin induces monocyte chemoattractant protein 1 and tissue factor expression in cultured vascular smooth muscle cells. *Arterioscler Thromb Vasc Biol*. 2003;23:1794-1800.
5. Cubeddu LX, Seamon MJ. Statin withdrawal: clinical implications and molecular mechanisms. *Pharmacotherapy*. 2006;26:1288-1296.
6. Upala S, Wirunsawanya K, Jaruvongvanich V, Sanguankee A. Effects of statin therapy on arterial stiffness: a systematic review and meta-analysis of randomized controlled trial. *Int J Cardiol*. 2017;227:338-341.
7. Rosengarten B, Auch D, Kaps M. Effects of initiation and acute withdrawal of statins on the neurovascular coupling mechanism in healthy, normocholesterolemic humans. *Stroke*. 2007;38:3193-3197.
8. Boesen ME, Singh D, Menon BK, Frayne R. A systematic literature review of the effect of carotid atherosclerosis on local vessel stiffness and elasticity. *Atherosclerosis*. 2015;243:211-222.
9. Kim HY, Lee SH, Heo JH, Kim MK, Park TH. Effect of statin withdrawal on carotid arterial distensibility. *J Neurosonol Neuroimag*. 2018;10:108-114.