Upregulation of Nitric Oxide, Inhibition of Oxidative Stress, and Antihypertensive Effects of Statins

To the Editor:

We read with great interest the article by Strazzullo et al1 in which they report a meta-analysis of 20 randomized, controlled trials of statin therapy and show that statins slightly but significantly reduced systolic blood pressure (−1.9 mm Hg in total patients and −4.0 mm Hg in the patients with systolic blood pressure >130 mm Hg).

Statins have pleiotropic effects on the vasculature, including upregulation of endothelial NO synthase expression and activity, downregulation of endothelin-1 and angiotensin II receptor subtype 1 expression, and inhibition of reduced nicotinamide-adenine dinucleotide phosphate oxidase activity, independent of their lipid-lowering effect.2 These pleiotropic vasoprotective effects may mediate, at least in part, the improvement in cardiovascular outcomes obtained with statin therapy. In the discussion of their findings, the authors hypothesized on the mechanisms underlying the antihypertensive effect of statins. In this regard, we have demonstrated that, in hypertensive Dahl salt-sensitive rats, a paradigm of salt-sensitive hypertension in humans, treatment with atorvastatin (30 mg per day per kilogram) for 10 weeks significantly reduced systolic blood pressure (174 ± 8 versus 200 ± 8 mm Hg in the hypertensive control rat) and end-organ injury (aortic and left ventricular hypertrophy and proteinuria).3 The reduction in systolic blood pressure was accompanied by normalization of endothelium-dependent relaxation to acetylcholine, restoration of vasoconstriction to endothelin-1, upregulation of vascular endothelial NO synthase activity, and inhibition of vascular oxidative stress (superoxide anion and isoprostanes). In the same animal model, inhibition of vascular superoxide anion production by either an inhibitor of NADPH oxidase or an angiotensin II receptor subtype 1 receptor blocker minimally reduced blood pressure, despite improving endothelial function and downregulating inflammatory gene expression.4,5 These studies suggest that control of oxidative stress alone does not suffice to produce a reduction in blood pressure. Vascular upregulation of NO synthesis is an adaptive response to the hemodynamic stress of increased blood pressure, and upregulation of endothelial NO synthase contributes to the reduction in vascular tone and to the prevention of pathological remodeling of the heart and vessels. However, whether endothelial NO is a friend or is in fact a foe depends on the concomitant production of superoxide anion in the microenvironment where NO is synthesized and released. In the presence of high superoxide anion, the bioactivity of NO is not only diminished but also transformed into peroxynitrite, an oxidant molecule with proatherogenic effects. Therefore, we surmise that upregulation of NO concomitantly with reduction of oxidative stress may importantly contribute to the antihypertensive effects of statins. Further studies are required to clarify the antihypertensive effect of statins and the underlying mechanisms.

Disclosures

None.

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5. Zhou MS, Adam AG, Jaimes EA, Raij L. In salt-sensitive hypertension, increased superoxide production is linked to functional upregulation of angiotensin II. Hypertension. 2003;42:945–951.

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