Statin Therapy: Having the Good Without the Bad

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Because serum cholesterol level is strongly associated with coronary heart disease, it has been generally assumed that cholesterol reduction by 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors or statins is the predominant mechanism underlying their beneficial effects. However, large prospective trials with statins suggest that these agents may have beneficial effects in cardiovascular disease in addition to their cholesterol-lowering effects. These so-called cholesterol-independent or “pleiotropic” effects include improving or restoring endothelial function, decreasing oxidative stress and inflammation, enhancing the stability of atherosclerotic plaques, and inhibiting the thrombogenic response in the vascular wall (Table). Many of these effects may explain some of the rapid actions of statin therapy on tissue perfusion in acute coronary syndrome and ischemic stroke, irrespective of baseline cholesterol levels.

Recently, statins have also been found to increase the number of circulating endothelial progenitor cells (EPCs).1 EPCs augment ischemia-induced neovascularization,2 accelerate re-endothelialization after carotid balloon injury,3 and improve post-ischemic cardiac function.4 Indeed, statins induce angiogenesis by promoting the proliferation, migration, and survival of circulating EPCs.5 In patients with stable coronary artery disease, administration of statins for 4 weeks augmented the number of circulating EPCs and enhanced functional capacity in patients with stable coronary artery disease.6 These findings agree with earlier data showing that statins rapidly mobilize EPCs from the bone marrow and accelerates vascular structure formation via activation of phosphatidylinositol 3-kinase/protein kinase Akt and endothelial nitric oxide synthase.5,7,8 These angiogenic effects appeared to have an antiangiogenic effect,9,10 suggesting a biphasic effect of statins on angiogenesis.11 However, this suggestion remains controversial since higher doses of statins have also been shown to be angiogenic.12

The clinical benefits of statins also extend beyond cardiovascular disease to include a reduction in the risk of dementia,13 Alzheimer disease,14 multiple sclerosis,15 osteoporosis,16 and possibly breast cancer.17,18 Indeed, there is growing evidence that the use of statins, either alone or in combination with other antitumor therapy, is associated with a decrease in the risk of cancer.19,20 However, because of the negative association epidemiologically between cancer and cholesterol levels, there remain concerns that the long-term use of statins may cause certain forms of cancer, especially in the elderly population as observed in the PROSPER trial.21,22

Herein lies the dilemma. Since the growth of tumors and atherosclerotic lesions is dependent on increased collateral blood supply,23,24 could statins, especially at lower concentrations, increase tumor growth and lesion size through their angiogenic effects? If so, this would greatly limit the therapeutic usefulness of statins in cardiovascular disease. In this issue of Hypertension, Sata et al12 provide convincing evidence that the beneficial effect of statins in augmenting collateral vessel growth to ischemic tissues was not associated with the development of cancer or worsening of atherosclerotic lesion. The uniqueness of this study was that ischemia-induced collateral growth and the development of cancer or atherosclerosis were temporally investigated in the same animal treated with statins. As expected, administration of low dose, and to a lesser extent, high dose statins increased capillary density and augmented collateral blood flow recovery to the ischemic hind limb of both wild-type and atherosclerosis-prone, apolipoprotein E–deficient (ApoE−/−) mice. However, treatment with statins did not increase collateral vessels or flow to implanted tumors, but instead, substantially retarded their growth. Similarly, statins increased angiogenesis to the ischemic hind limb and inhibited the development of atherosclerotic lesions in ApoE−/− mice. These findings suggest that angiogenesis in response to ischemia may be mechanistically different compared with that of tumor growth and atherosclerotic lesion progression. Nevertheless, inhibition of collateral flow to cancers and atherosclerotic lesions has been shown to decrease tumor and plaque growth.23,24

In summary, statins are protective in cardiovascular disease, possibly through their ability to augment collateral blood flow to ischemic tissues in a cholesterol-independent manner. This selective proangiogenic effect on ischemic tissues occurs without increasing tumor growth or atherosclerotic lesion size. It is not known, however, whether these observations also apply to other pathological conditions such as diabetic retinopathy where enhancing neovascularization could actually worsen the disease. Thus, further studies are needed to understand exactly how statins promote angiogenesis in ischemic tissues but not in tumors. Perhaps factors in the ischemic environment are much more favorable to EPC recruitment and survival than that of tumors. Given the therapeutic implications of statin therapy, the answers to these questions will likely yield important new insights into
Effects of Statins on the Vascular Wall

Endothelial function
-↑ Endothelial nitric oxide synthase expression and activity
-↑ Angiogenesis
-↑ Circulating endothelial progenitor cells
-Endothelin-1 synthesis and expression
-↑ Reactive oxygen species
-↓ Angiotensin type-1 receptor expression
-↓ Adhesion molecule expression
-↓ Leukocyte-endothelial cell adhesion
-Inducible nitric oxide synthase expression
-↓ Proinflammatory cytokines (tumor necrosis factor-α, interleukin-1, interleukin-6) expression
-↓ monocytechoaottractant protein-1 secretion
-↓ Interleukin-8 secretion

Inflammation
-↓ Macrophage growth
-↓ Matrix metalloproteinase expression and secretion
-↓ Tissue factor expression and activity
-↓ Major histocompatibility class II antigen expression
-↓ Scavenger receptor expression

Thrombosis
-↓ tissue-type plasminogen activator expression
-↓ Plasminogen activator inhibitor-1 expression
-↓ platelet reactivity
-↓ Thromboxane A₂ biosynthesis

Plaque stabilization
-↑ Bone formation
-↓ Tumor growth

additional factors and conditions that regulate angiogenesis. This hopefully will lead to the development of novel therapeutics not only in cardiovascular medicine, but also in cancer biology. Only then can we hope to have our cake and eat it too.

References


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