Biphasic Effects of Statins on Angiogenesis

To the Editor:

I read with interest the recent article by Weis et al. that investigated the effects of HMG-CoA reductase inhibitors, or statins, on angiogenesis in vitro and in vivo. The report, along with recent publications, raised clinical interest in the potential use of statins for therapeutic angiogenesis to treat patients with ischemic diseases. On the other hand, there is a growing concern that statins may promote tumor growth, diabetic retinopathy, and atherosclerosis, by stimulating angiogenesis. If this were the case, we should reconsider the clinical use of statins, although recent evidence suggests that statins exert a number of beneficial effects, even in normocholesterolemic patients.

Statins have been widely used to lower cholesterol levels for >10 years without serious adverse effects. There is no clinical evidence that statins increase the morbidity of cancer, diabetic complications, or myocardial infarction. Conversely, it has been suggested that statins suppress pathological angiogenesis such as neovascularization in atherosclerotic plaques or tumors at clinically relevant doses. A randomized controlled trial revealed that pravastatin prolongs survival of patients with advanced hepatocellular carcinoma.

To explain the puzzling effects of statins on angiogenesis, Weis et al propose a biphasic dose-dependent effect of statins on angiogenesis, ie, proangiogenic at low therapeutic doses (0.5 mg/kg/d of cerivastatin), but angiostatic at high doses (2.5 mg/kg/d), based on their observations in mouse models of inflammation and tumor-induced angiogenesis. On the contrary, my colleagues and I have previously reported that cerivastatin-induced collateral vessel growth in response to acute ischemia had been induced (Sata et al, unpublished observation, 2002). Therefore, one might speculate that chronic exposure to high-dose statins would have angiostatic effects in our patients. This property of statins promote the migration of mature endothelial cells and endothelial progenitor cells at low concentrations, whereas antiangiogenic effects were achieved at high concentrations (>0.1 \( \mu \)mol/L atorvastatin).

One crucial question remains: Are human statin concentrations proangiogenic or antiangiogenic? Serum levels of statins in humans range between 0.002 and 0.1 \( \mu \)mol/L. In our in vitro studies, proangiogenic effects were observed at statin concentrations between 0.005 and 0.05 \( \mu \)mol/L (low-to-midrange concentrations in humans). Therefore, one might speculate that chronic exposure to high-dose statins would have angiostatic effects in our patients. This property of the statins might explain in part their beneficial effect on atherosclerotic plaque, the growth of which is dependent on neovascularization.

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Circulation. 2002;106:e47
doi: 10.1161/01.CIR.0000030081.54465.2D
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/106/11/e47

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