

## Angiogenesis and Statins: the Highest the Dose, the Best?

To the Editor,

We read with great interest the excellent review article by Llevadot and Asahara on the effect of statins in angiogenesis.<sup>1</sup> Although it was suggested that angiogenesis might be involved in the progression of coronary lesions,<sup>2</sup> as its name indicates, this is a complex process that leads to the formation of new vessels from preexisting ones.<sup>3</sup> Thus, induction of angiogenesis by this group of drugs may be just another of their various nonlipidic properties,<sup>4</sup> such as improved endothelial function, reduced inflammatory response and attenuated plaque thrombogenicity. These effects may be involved in the clinically observed benefits in both primary and secondary prevention in clinical trials that have tested statins.

In recent years proof of the benefits of greater reductions in lipid levels as a result of increased doses of statins<sup>5</sup> has raised the following questions: do the benefits increase with decreasing lipid levels? Do they increase with higher doses of statins?

Hypercholesterolemia has been seen to lead to worsening angiogenesis.<sup>6</sup> In their review, Llevadot and Asahara<sup>1</sup> show how statins reverse this condition. However, the considerable antiinflammatory effect of statins<sup>7</sup> may have important consequences, which are not always favorable. When attacked, the endothelium undergoes functional and structural changes. In principle the inflammatory response is beneficial in protecting the individual against noxious agents. Ischemia and inflammation are among the main angiogenesis-stimulating agents.<sup>8</sup> Thus, in patients with coronary arteriosclerosis, suppressing the «adaptive» inflammatory mechanism might delay the development of collateral circulation in response to episodes of ischemia. Experimental studies recently showed that statins can have a biphasic effect on angiogenesis.<sup>9,10</sup> At low doses they increased angiogenesis, whereas this effect was significantly reduced at higher doses. These findings confirm the need for further studies to analyze the effect of high doses of statins in humans, and to evaluate their long-term clinical benefits.

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