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Reply to the Editor:

Statins are increasingly being used in patients with coronary disease. Recently, there has been increasing evidence from studies conducted in both in vitro and murine models that low-dose statins promote angiogenesis and high-dose statins inhibit it.¹ The application of these findings to patients is limited because of the lack of translation of the experimental models to the human setting. It is in this context that we examined the in vivo effects of high-dose atorvastatin in a clinically relevant large animal model of chronic myocardial ischemia and hypercholesterolemia. We found that atorvastatin treatment did not improve endogenous myocardial angiogenesis² or response to growth factor therapy,³ despite improvement in endothelial function.

Czepluch and Waltenberger make the important point that the dose of statins used may be too high for clinical relevance and indeed may be toxic. The first thing to note is that, for initial toxicity studies, as much as 80 mg/kg of atorvastatin was given to

beagle dogs without any observable adverse effects,⁴ versus the dose of 3 mg/kg used in our study. Second, when embarking on these studies, our objective was to choose a dose that would provide meaningful reductions in total cholesterol and low-density lipoprotein cholesterol in light of the model of potent diet-induced hypercholesterolemia being used. Finally, a number of groups have demonstrated that Akt activation in response to atorvastatin exposure occurs in a time-dependent manner; this has been demonstrated in in vitro studies at both low and high doses. We have shown that this Akt activation also occurs in vivo in the myocardium, and although it may have detrimental effects, Akt activation is not in and of itself indicative of statin overdose.

Czepluch and Waltenberger appropriately point out that similar experiments conducted in the setting of normocholesterolemia and a lower, more clinically relevant statin dose would help to validate our findings. Indeed, we have recently performed experiments examining a lower statin dose (1.5 mg/[kg · d], equivalent to 80 mg/d in humans), used routinely in the clinical setting, in normocholesterolemic swine (abstract presented at the American Heart Association, Scientific Sessions 2005, manuscript currently under review). We found that atorvastatin treatment (1.5 mg/[kg · d] for 20 weeks) was associated with reduced collateral-dependent myocardial perfusion and reduced endothelial cell density in the ischemic territory of normocholesterolemic swine relative to control swine. These animals also demonstrated impaired coronary microvessel relaxation in response to growth factors (vascular endothelial growth factor and fibroblast growth factor) as well as increased myocardial expression of antiangiogenic protein (endostatin). These findings provide substantial support to the idea that high-dose statins can impair the myocardial angiogenic response.

In light of the mounting evidence from in vitro and now in vivo large animal studies regarding the antiangiogenic effects of high-dose statins, it is crucially important to determine the relevance of these studies to patients with coronary disease. It may be that the metabolism of atorvastatin or the signaling pathways leading to collateral growth are different in pigs than in human beings. Yet most preclinical research is

currently performed in this species. The beneficial effects of statins on clinical outcomes have been well demonstrated in large clinical trials. One proposed mechanism for their cholesterol-independent effects is plaque stabilization, which may occur through the inhibition of plaque angiogenesis. There is also emerging recognition, in the literature, of a possible benefit of statins in reducing the incidence and progression of neoplastic processes, which may also be secondary to their antiangiogenic effects. Finally, drug-eluting stents clearly reduce the incidence of restenosis. Yet there is recent evidence that collateral growth is impaired by these stents.⁵ Thus, the likelihood of vascular occlusion may be less with these stents, but if it does occur, there may not be as much collateral reserve, leading to a high incidence of stent thrombosis-related death (>40%).

The study of new vessel formation in the myocardium is a challenging task that is limited by currently available imaging modalities (eg, angiography, nuclear imaging, positron emission tomography). Thus any definitive conclusions regarding the applicability of these findings to the clinical setting would first require rigorously designed randomized clinical trials with appropriately selected end points. These studies would more clearly define the risks and benefits of statins, which are increasingly being used at high doses and for indefinite periods. If proved in clinical studies, the antiangiogenic properties of statins would have to be incorporated in the risk-benefit assessment for the initiation and maintenance of statin therapy in patients with coronary disease, in whom collateral vessel formation can be a lifesaving process.

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Off-pump coronary bypass surgery, graft patency, and the need of an informed consent

To the Editor:

We read with interest the article by Lim and colleagues¹ concerning graft patency after off-pump coronary bypass surgery (OPCAB). They showed that both patency and number of distal anastomoses are lower in OPCAB, which confirms and ex-

tends previous evidence published by our group concerning reduced patency rates.²⁻⁴

The OPCAB technique was developed and reintroduced in the clinical practice for economic reasons in some southern America countries more than a decade ago, and then it became progressively adopted by European and North America centers to reduce trauma, thus rendering coronary bypass surgery an easier choice compared with less invasive options (eg, interventional cardiologic procedures).

In recent years, evidence has accumulated concerning both the pros and cons of the OPCAB approach. It is now well established that OPCAB is associated with a reduced rate of minor outcomes such as the incidence of postoperative atrial fibrillation, the need of blood products, and probably reduced myocardial enzyme release.⁴ On the other hand, the risk of reduced patency and reduced revascularization is an important issue of OPCAB procedures. Thus, patients should be extensively informed about the pros and cons of the OPCAB approach before surgery, and they should clearly express their acceptance to undergo OPCAB.

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