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Reply to the Editor:

We thank Pocar and colleagues for their interest in our article regarding surgery for acute type A aortic dissection in the setting of stroke.¹ We also acknowledge their recent report about repairing acute type A aortic dissection in patients with coma.² As was pointed out in their report, the use of the Glasgow Coma Scale (GCS) to exclude patients for type A aortic repair was not relevant. Specifically, they noted that all 5 of their patients would have been considered severely brain injured (GCS < 8) based on the GCS alone. We do appreciate and concur with this point and also congratulate them for their results in this very difficult subgroup of patients.

Although the GCS, the National Institutes of Health Stroke Scale (NIHSS), and Rankin score for that matter may not be completely applicable in the setting of acute type A aortic dissection, we wanted to analyze these patients with objective criteria. We do believe that the NIHSS and the Rankin score may be helpful, although this study was not powered to demonstrate this. Because we recommended that operative repair was indicated in patients without "neurologic devastation" or coma, we attempted to provide some objective criteria for this condition, hence the use of these scales and scores. Regarding the 1 nonoperated patient who was considered neurologically devastated, we acknowledge that one cannot derive any conclusions in relation to defining neurologic devastation. In fact, it was the appearance of the patient's computed tomography scan of the head, which showed bilateral massive infarction, that ultimately led to his nonoperative course.

Prior to the results of this study, we maintained that stroke was a relative contraindication to immediate repair for acute type A aortic dissection. We have since

modified our approach and have become more aggressive in repairing acute type A aortic dissection in patients with stroke. Our experience in patients with coma, however, has been limited and thus we continue to maintain a selective approach in patients with coma and neurologic devastation. We admit that GCS is not a good measure of coma or neurologic devastation, and radiographic evaluation, in the hemodynamically stable patient, may be more helpful. How coma and neurologic devastation are determined and whether or not surgery is performed, however, should be left ultimately to the neurologist and operating surgeon, respectively.

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High-dose atorvastatin is associated with impaired myocardial angiogenesis in response to vascular endothelial growth factor in hypercholesterolemic swine: Relevance to the human situation?

To the Editor:

We read with great interest the article by Boodhwani and colleagues¹ regarding the impact of high-dose statin therapy on vascular endothelial growth factor-A (VEGF-A)-induced myocardial angiogenesis in a hypercholesterolemic pig model of chronic ischemia. This article demonstrated that collateral-dependent myocardial perfusion remained impaired in hypercholesterolemic and atorvastatin-treated pigs in response to additional treatment with VEGF-A relative to a normocholesterolemic control group. It concluded that a high-dose statin therapy was not associated with improved myocardial neovascularization. In that study, however, the hypercholesterolemic pigs were treated with an atorvastatin dosage

of 3 mg/(kg · d), which exceeds the maximal possible dosage in patients (80 mg/d) by a factor of about 3.

To achieve at least moderate cholesterol lowering, pigs need to be treated with high-dose statins because of lesser lipid-lowering potency and efficacy in pigs relative to human beings.² One must remain aware, however, of the increased risk of adverse events with extremely high statin dosages. In their article, Boodhwani and colleagues¹ described a clearly decreased capillary endothelial cell density in the ischemic territory in the hypercholesterolemic and atorvastatin-treated pigs relative to the normocholesterolemic pigs and even the untreated hypercholesterolemic animals. To exclude the possibility that the hypercholesterolemic and atorvastatin-treated pigs suffered potential toxic (cellular) side effects of atorvastatin that might explain the neovascularization impairment, the investigators should have incorporated a control group of normocholesterolemic pigs treated with the same atorvastatin dosage. Moreover, treatment of the hypercholesterolemic pigs with lower atorvastatin dosages, more relevant to the human situation, might demonstrate whether there are potential dose-dependent toxic cellular side effects. Indeed, a recently published article by Chade and associates³ indicates that statins used in an intermediate (human) dosage in pigs do lead to a stimulation of arteriogenesis. Furthermore, a retrospective clinical study supports the view that intensified statin treatment is associated with an improved arteriogenic response in human beings.⁴

Another piece of evidence for statin overdose in the hypercholesterolemic pigs of Boodhwani and colleagues¹ might be the observation of prolonged Akt activation in the atorvastatin-treated pigs. Therefore, the Akt downstream signal transduction pathways in endothelial cells might not any longer be able to respond adequately to other pathophysiologic stimuli. Indeed, it has been demonstrated that a prolonged Akt activation is associated with detrimental cardiac effects in an ischemic mouse model,⁵ as was even cited by Boodhwani and colleagues¹ in their article.

Taken together, we believe that it is not appropriate to compare directly the arteriogenic effects of high-dose statin treatment in pigs and human beings in light of the approximately 3-fold higher statin dosage used in pigs.

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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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