We are grateful for the comments of Dr. Thombs and colleagues.

In our recent study we set out to examine the effects of the timing of assessment of depression on mortality after myocardial infarction (MI) (1). We showed that depression before MI, whether chronic or not, does not increase cardiac mortality. This was a surprise to us because we anticipated that pre-MI depression, whether chronic or not, does not increase cardiac mortality. Patients developing depression in the period immediately after MI that are at increased risk of cardiac mortality. Patients developing depression after an acute cardiac event have been shown to be at increased risk of dying in previous studies (4,5), and we are now looking at this particular question in our own data.

Our negative findings for depression cannot be dismissed as resulting from our statistical methods. We accept the point that the number of independent variables included was large, but our finding was the same in the uncontrolled (univariate) comparison. Furthermore, our findings remained stable if we used backward elimination of variables, so that the number of independent variables in the final model was few (hazard ratio [HR] for depression = 0.86, p = 0.60) or if we performed our analyses using fewer variables (e.g., age, gender, educational level, degree of cardiac dysfunction, and revascularization procedures (4), HR for depression = 1.02, p = 0.94). Our findings also remained negative when we did not control for medications at discharge (HR for depression = 0.87, p = 0.62).

Our finding that subjects with depression at both baseline and 12 months had an apparent survival advantage is confusing and counterintuitive. We can clarify here that, compared with the remainder, this group was more likely to be female gender (49% vs. 28%) and younger (mean age 45.3 vs. 60.8 years). Controlling for age and gender alone eliminated the association between persistent depression and subsequent mortality (p = 0.97).

The fact that depression that predates the MI and persists through the post-MI period does not predict mortality is extremely important. It supports the suggestion that it is not depression alone that is having the adverse impact on survival but that some additional factor interacts with depression to create this effect (6,7). Rather than ignoring the heterogeneity in previous findings, future research should continue to examine possible reasons for this heterogeneity as it may identify vulnerable subgroups and explain how and why depression has this effect on survival.

Chris Dickens, PhD
Barbara Tomenson, MSc
Francis Creed, MD

Department of Psychiatry
Rawnsley Building
Manchester Royal Infirmary
Oxford Road
Manchester M13 9WL
United Kingdom
E-mail: chris.dickens@manchester.ac.uk

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Eliminating Plaque Angiogenesis

We have read with great interest the article by Kolodgie et al. (1) focusing on elimination of intraplaque angiogenesis. It seems that neovascularization within the vessel wall plays an important role in plaque destabilization, and it is a determinant of vulnerability.

The beneficial effect of statins in patients with atherosclerotic disease is well established. This effect goes beyond lipid lowering, because statins also have other effects, which is why statins are considered pleiotropic. One of these is its effect on angiogenesis. We recently presented that patients on statin treatment have decreased intraplaque angiogenesis in their carotid endarterectomy specimens when compared with patients not receiving this kind of drug (2). This finding provides a new insight to the statins’ pathophysiological mechanism of action. The fact that it was a
cross-sectional, retrospective study without randomization cannot lead us to any causal conclusions about statins and intraplaque angiogenesis. However, there are strong indications favoring that hypothesis. Vascular endothelial growth factor is a well-recognized and potent angiogenic factor. It is known that pravastatin, but also fenofibrate, reduces vascular endothelial growth factor plasma levels in humans (3).

These findings raise the question of whether statins are the angiogenic factor for which we are searching. To answer this question, further investigation is needed, and maybe it is time for a randomized trial with standard dose and duration of treatment to test the effect on intraplaque angiogenesis.

Michael Koutouzis, MD
*Zenon S. Kyriakides, MD, PhD

*Director, B Cardiology Department
Red Cross Hospital
1 Red Cross Str.
Athens 115 26
Greece
E-mail: zskyt@otenet.gr

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Reply

Koutouzis et al. (1) propose the paradigm of statins eliminating plaque angiogenesis and, thus, lesion instability. These authors recently showed pathologic data of reduced microvascular density in carotid plaques from patients receiving statins at least 3 months. However, direct evidence of decreased intraplaque angiogenesis attributed to statins and clinical improvement is lacking. Moreover, magnetic resonance imaging shows statins to be more effective in debulking nonhemorrhagic plaques as necrotic core volume in lesions with intraplaque hemorrhage increases, despite statin use (2). Large-scale clinical trials in parallel angiogenic disorders such as age-related macular degeneration (3) or tumor growth (4) have failed to show a consistent association between statins and disease regression. These results are in opposition to the potent antiangiogenic effects of statins in angiogenic assays (5) or animal models (6).

Although statins down-regulate various gene products that mediate cell proliferation, including vascular endothelial growth factor (7), there is an increasing redundancy of angiogenic factors creating the potential to circumvent drugs targeting specific pathways (8). Further, the expression of pro- and antiangiogenic mediators is likely dependent on lesion stage, possibly compromising the efficacy of a single drug. The identification of reliable biomarkers or imaging methods to gauge the effectiveness of antiangiogenic therapy also remains an obstacle because the current end point is limited to evaluation of surgical tissue.

Finally, it is not clear whether decreased neovascularization or “normalization” of existing vessels is the more favorable approach because the pathology is not dictated by the mere presence of vessels, but by the fact that these structures are dysfunctional as they are fragile and leaky. A normalized, less leaky vasculature, characterized by a more restrictive basement membrane surrounded by pericytes (9), may support a more favorable microenvironment promoting plaque stabilization.

Frank D. Kolodgie, PhD
Jagat Narula, MD, PhD, FACC
Chun Yuan, PhD
Aloke V. Finn, MD
Herman K. Gold, MD, FACC
*Renu Virmani, MD, FACC

*CVPath Institute, Inc.
19 Firstfield Road
Gaithersburg, Maryland 20878
E-mail: rvirmani@cvpath.org

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