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Reply

We agree with Dr. Manev and colleagues that our study (1) does not rule out the possibility that inflammatory pathways alternative to those pertinent to the common biomarkers C-reactive protein (CRP) and interleukin (IL)-6 may be involved in the link between depression and cardiovascular disease (CVD). Depression is associated with a number of inflammatory markers in addition to CRP and IL-6, including, for example, IL-1 beta and tumor necrosis factor alpha (2). The list may well include 5-lipoxygenase (5-LOX), but unfortunately this has not yet been described, at least in humans. C-reactive protein and IL-6 are the 2 biomarkers most consistently associated with cardiovascular risk and therefore it makes sense to begin with these as we try to disentangle the complex link between depression, inflammation, and CVD. Because they are produced as part of the acute phase response, it is possible that these common biomarkers are not truly biologic markers for depression. On the other hand, inflammatory cytokines have well-characterized effects in the central nervous system that may influence depressive behavior, including effects on neurotransmitter function and stimulation of the hypothalamus-pituitary-adrenal axis (3). These actions suggest that inflammatory processes are central to the pathogenesis of depression similar to many other chronic conditions, such as CVD. It is also possible that inflammation contributes to some, but not all, cases of depression, as suggested by the wide range of inflammatory activity commonly found in samples of depressed individuals. Thus, subsets of individuals at the upper end of cytokine levels could drive most of the association (4).

Dr. Manev and colleagues suggest a central role of an up-regulated leukotriene synthesis pathway in the link between depression and CVD. We agree with this possibility. A number of genetic variations in the arachidonic acid cascade leading to leukotriene synthesis have been linked to the risk of myocardial infarction and increased carotid atherosclerosis (5–7). Unfortunately, no data are yet available regarding the relationship between 5-LOX, or other components of this metabolic pathway, and depression in humans. Until these data become available, this biologic mechanism remains speculative.

We agree with Dr. Manev and colleagues that future studies addressing the interconnections between depression, inflammation, and CVD should include a wider selection of inflammatory markers that may be relevant to both atherosclerosis and depression; 5-LOX should be one of these. At the current stage of knowledge, we believe that no inflammatory biomarker can be credibly considered to be more than just a correlate of depression.

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Are Surrogate End Points in Drug-Eluting Stent Trials Reliable?

We read with great attention the paper by Pocock et al. (1). We welcome their thorough analysis; however, we have a few concerns related to some methodologic aspects of the manuscript.

The first relates to the assessment of treatment differences among angiographic or clinical end point selected with the z-score. We believe the authors should also report the rates of target lesion revascularization (TLR) in the patients who were not supposed to receive angiographic follow-up in the trials where a control angiogram was mandated only in a subgroup of patients. This would allow comparing the difference among stents ("delta") in TLR rate between the angiographic and the clinical cohorts and indirectly comparing the "delta" in late loss (LL) and percentage diameter stenosis (%DS) with the "delta" in TLR in the clinical cohort. Indeed, despite the fact that the authors already acknowledged in their discussion that systematic angiographic follow-up can increase the rate of TLR, it would be useful to systematically quantify this phenomenon and to observe if it can impact the treatment differences between devices.

The second concern refers to the relationship between the size of treatment effect on TLR and on LL/%DS, using the Hughes criterion of surrogacy by visually plotting mean LL or %DS and TLR rate. The authors should limit this analysis only to the