5. Firuzi O, Zhuo J, Chinnici CM, Wisniewski T, Praticò D. 5-lipoxygenase gene disruption reduces amyloid-β pathology in a mouse model of Alzheimer's disease. FASEB J 2008;22:1169–78.
6. Manev R, Imbesi M, Uz T, Dzitoyeva S, Dimitrijevic N, Manev H. Effects of 5-lipoxygenase inhibitors MK-886 and caffeic acid in a model of forced swimming in wild-type and 5-lipoxygenase–deficient mice. Program 711.4/BB17. 2007 Neuroscience Meeting Planner. San Diego, CA: Society for Neuroscience, 2007. Available at: http://www.abstractsonline.com/viewer/viewAbstractPrintFriendly.asp?CKey={B531E434-A1EE-476C-9071-52AC68106587}&SKey={531A911D-5233-4F6D-99FB-928B3456C2F8}&MKey={FF8B70E5-B7F9-4D07-A58A-C1068FDE9D25}&AKey={3A7DC0B9-D787-44AA-BD08-FA7BB2FE9004}. Accessed March 27, 2008.
7. Stewart JC, Janicki DL, Muldoon MF, Sutton-Tyrrell K, Kamarck TW. Negative emotions and 3-year progression of subclinical atherosclerosis. Arch Gen Psychiatry 2007;64:225–33.

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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REFERENCES

1. Vaccarino V, Johnson BD, Sheps DS, et al. Depression, inflammation, and incident cardiovascular disease in women with suspected coronary ischemia: the National Heart, Lung, and Blood Institute–sponsored WISE study. J Am Coll Cardiol 2007;50:2044–50.
2. Irwin M. Psychoneuroimmunology of depression: clinical implications. Brain Behav Immun 2002;16:1–16.
3. Raison CL, Capuron L, Miller AH. Cytokines sing the blues: inflammation and the pathogenesis of depression. Trends Immunol 2006;27:24–31.
4. Tiemeier H, Hofman A, van Tuijl HR, Kiliaan AJ, Meijer J, Breteler MM. Inflammatory proteins and depression in the elderly. Epidemiology 2003;14:103–7.
5. Dwyer JH, Allayee H, Dwyer KM, et al. Arachidonate 5-lipoxygenase promoter genotype, dietary arachidonic acid, and atherosclerosis. N Engl J Med 2004;350:29–37.
6. Helgadottir A, Manolescu A, Helgason A, et al. A variant of the gene encoding leukotriene A4 hydrolase confers ethnicity-specific risk of myocardial infarction. Nat Genet 2006;38:68–74.
7. Helgadottir A, Manolescu A, Thorleifsson G, et al. The gene encoding 5-lipoxygenase activating protein confers risk of myocardial infarction and stroke. Nat Genet 2004;36:233–9.

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

drug-eluting stent (DES) arms of the trials, avoiding inclusion of the bare-metal stent (BMS) arms. Indeed, much of the visual assessment of the relationships shown seems dependent on the BMS arms of the trials included. We believe that the relationship between mean LL and TLR rate is a crucial point in clinical practice to decide which DES performs better and in the development of new DES to understand whether a new device can compete with the ones already on the market. Thus a more accurate and definitive analysis of this correlation should be clearly made and should only include patients treated with DES. In light of this, the authors correctly recognized that, in the REALITY (Prospective Randomized Multi-Center Head-to-Head Comparison of the Sirolimus-Eluting Stent [Cypher] and the Paclitaxel-Eluting Stent [Taxus]) trial (2), which directly compared 2 DES, the TLR rates were similar despite a highly significant difference in LL and %DS. We suggest a possible explanation for this apparent paradox. Bare metal stents have been shown to have a bimodal distribution of angiographic measures of restenosis (3). We have suggested that this distribution can be possible also with DES (4,5). Sirolimus-eluting stents showed a sort of "all-or-none" phenomenon, having a very low average LL driven by the lack of LL in nonrestenotic lesions. Paclitaxel-eluting stents, in contrast, accommodated some LL also in nonrestenotic lesions and this led to a higher average LL value.

We urge the authors to test again this hypothesis and to perform a detailed analysis of the distribution of LL and %DS, given the large database of prospectively enrolled patients with independently performed quantitative coronary angiographic analysis that they can access. If the bimodal distribution of angiographic parameters of restenosis were confirmed also for DES, this could have a major impact in the design, analysis, and conduct of future comparative DES trials.

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REFERENCES

1. Pocock SJ, Lansky AJ, Mehran R, et al. Angiographic surrogate end points in drug-eluting stent trials: a systematic evaluation based on individual patient data from 11 randomized, controlled trials. J Am Coll Cardiol 2008;51:23–32.
2. Morice MC, Colombo A, Meier B, et al., REALITY Trial Investigators. Sirolimus- vs. paclitaxel-eluting stents in de novo coronary artery lesions: the REALITY trial: a randomized controlled trial. JAMA 2006;295:895–904.
3. Schomig A, Kastrati A, Elezi S, et al. Bimodal distribution of angiographic measures of restenosis six months after coronary stent placement. Circulation 1997;96:3880–7.
4. Cosgrave J, Melzi G, Corbett S, et al. Comparable clinical outcomes with paclitaxel- and sirolimus-eluting stents in unrestricted contemporary practice. J Am Coll Cardiol 2007;49:2320–8.
5. Agostoni P, Cosgrave J, Biondi-Zoccai GG, et al. Angiographic analysis of pattern of late luminal loss in sirolimus- and paclitaxel-eluting stents. Am J Cardiol 2007;99:593–8.

Reply

We appreciate the insightful comments of Drs. Agostini and Biondi-Zoccai about our study (1). Regarding their first point, we felt it was relevant to concentrate on the direct comparisons of late loss (LL) and percentage diameter stenosis (%DS) with target lesion revascularization (TLR) in the same patients. We recognize the potential impact of the oculostenotic reflex on risk of TLR, but can confirm that the treatment differences in TLR in angiographic and clinical cohorts were in fact similar in those large trials with over 150 patients in both cohorts (DELIVER, ENDEAVOR II, SIRIUS, and TAXUS IV). We have also previously reported that in the TAXUS IV trial routine angiographic follow-up increased TLR rates by approximately 40%, though to a similar degree with bare-metal stents (BMS) and drug-eluting stents (DES) (2).

Regarding their second point, we distinguish between DES and BMS arms in the visual plots of mean LL or %DS and TLR rates, so readers can readily assess the association for DES arms alone. In the 11 trials, the distributions of LL in both the DES and BMS arms are not bimodal but somewhat skewed to the right.

That is why we propose the use of the predictive formulas in the Appendix to work out what TLR rate one expects for a given DES, given the observed distributions (rather than just the mean) of LL or %DS.

We have an alternative explanation for the apparent paradox whereby highly significant differences in LL and %DS for 2 different DES nevertheless lead to somewhat similar TLR rates. The logistic curvilinear relation between TLR and LL means that the majority of patients will have LL at the rather flat left-hand end of the curve, and therefore there is little difference in risk of TLR in such patients. Thus a highly significant difference in LL between 2 stents but with typically low LL in most patients can be expected to lead to a rather small (but real) difference in true TLR rates. However, most trials are of insufficient size to distinguish such small true differences from the null hypothesis of no difference. That is why we believe insight into vessel-related efficacy is best done first with fairly small trials based on these surrogates, to be followed by much larger simpler trials, without planned follow-up angiograms, to evaluate patient-oriented stent safety.

Finally, we do believe that rare phenomena such as strut fracture or hypersensitivity reactions may occasionally result in restenosis unrelated to the logistic equations we have proposed. These, however, are unusual occurrences, and as such LL and %DS may be used as angiographic surrogates for the clinical event TLR.

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REFERENCES

1. Pocock SJ, Lansky AJ, Mehran R, et al. Angiographic surrogate end points in drug-eluting stent trials: a systematic evaluation based on individual patient data from 11 randomized, controlled trials. J Am Coll Cardiol 2008;51:23–32.
2. Ellis SG, Popma JJ, Lasala JM, et al. Relationship between angiographic late loss and target lesion revascularization after coronary stent implantation: analysis from the TAXUS-IV trial. J Am Coll Cardiol 2005;45:1193–200.