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.
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.

*Pierfrancesco Agostoni, MD
Giuseppe G. L. Biondi-Zoccai, MD

*Antwerp Cardiovascular Institute Middelheim
AZ Middelheim
Lindendreef 1
2020 Antwerp
Belgium
E-mail: agostonipf@gmail.com

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Reply

We appreciate the insightful comments of Drs. Agostoni 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 occlusostenotic 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 (DELIBER, 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.

Stuart J. Pocock, PhD
Martin P. Fahy, MSc
Roxana Mehran, MD, FACC
*Gregg W. Stone, MD, FACC

*The Cardiovascular Research Foundation
Columbia University Medical Center
111 East 59th Street
11th Floor
New York, New York 10022
E-mail: gs2184@columbia.edu

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