REFERENCES

1. The Hypothermia After Cardiac Arrest Study Group. Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. N Engl J Med 2002;346:549–56.
2. Bernard SA, Gray TW, Buist MD, et al. Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia. N Engl J Med 2002;346:557–63.
3. Boddicker KA, Zhang Y, Zimmerman MB, Davies LR, Kerber RE. Hypothermia improves defibrillation success and resuscitation outcomes from ventricular fibrillation. Circulation 2005;111:3195–201.
4. Abella BS, Zhao D, Alvarado J, Hamann K, Vanden Hoek TL, Becker LB. Intra-arrest cooling improves outcomes in a murine cardiac arrest model. Circulation 2004;109:2786–91.

Letters to the Editor

Depression, Inflammation, and Cardiovascular Disease

Is 5-Lipoxygenase the Missing Link?

In a study recently published in the *Journal*, Vaccarino et al. (1) concluded that despite the significant comorbidity of depression with inflammation and of depression with cardiovascular disease (CVD), the inflammatory biomarkers C-reactive protein (CRP) and interleukin (IL)-6 could account for only a small portion of the association between depression and CVD. Therefore, using these 2 biomarkers of inflammation, the study found that, for the most part, depression and inflammation influence CVD risk through independent pathways. The authors contrasted the multifactorial link between depression and CVD to the robust and prognostic association of these 2 inflammatory biomarkers with depression as a possible reason that there is only a weak link of these biomarkers to CVD associated with depression. We would like to suggest an alternative explanation.

Recently, it was proposed that 5-lipoxygenase (5-LOX) provides a biologic link between depressive symptoms and atherosclerosis (2). 5-Lipoxygenase is an inflammatory enzyme responsible for the synthesis of arachidonic acid metabolites, that is, leukotrienes. Increased activity of the 5-LOX pathway, which includes another protein termed FLAP (5-lipoxygenase–activating protein), is strongly associated with atherosclerosis and elevated CVD risks, including that for stroke (3). In addition to its presence in the cardiovascular system, 5-LOX is expressed in the brain (4), where its functioning may be independent of cardiovascular activity. In the brain, 5-LOX participates in the regulation of neurotransmitter receptors, e.g., glutamate (2), and influences amyloid-beta deposition (5). Pharmacologic 5-LOX inhibition is being considered as therapy for atherosclerosis and CVD. Interestingly, in an animal model of depression, 5-LOX inhibition produces antidepressant-like effects (6). Therefore, it was proposed that 5-LOX may be a common biologic mechanism involved in both atherosclerosis and depression (2).

C-reactive protein and (IL-6 are only 2 of the numerous molecules that may be associated with inflammation. It is possible that their abundance in peripheral samples such as the plasma is not proportionally or equally related to the severity and progression of various pathobiologic processes, for example, inflammation, CVD, and depression. Moreover, whereas the mechanistic association of these 2 molecules with inflammation and atherosclerosis appears straightforward, it is unclear how they might modify neuronal functioning, suggesting that in depression they are not a direct biologic marker. In fact, currently there are no reliable direct biologic markers for depression.

Nevertheless, it could be that when up-regulated, a common biologic pathway participates in inflammation, atherosclerosis, and depression, albeit by recruiting different effectors. For example, activation of cardiovascular 5-LOX may lead to inflammation of the blood vessel wall and consequent atherosclerosis. In the brain, activation of 5-LOX may contribute to lower phosphorylation and membrane insertion of glutamate receptors type 1 (GluR1); decreasing 5-LOX activity and increasing GluR1 phosphorylation may be antidepressant. If a common mechanism, such as proposed here for 5-LOX, is indeed operative, one would expect that subtle changes in such a mechanism, for example, due to genetic variability (3), may influence blood vessels and brain functioning even in the absence of major alterations of biomarkers such as CRP and IL-6. Supporting this possibility is the observation of an association between depressive symptoms in clinically nondepressed subjects and the progression of subclinical atherosclerosis (7). By excluding CRP and IL-6 as common biologic markers, the report by Vaccarino et al. (1) provides impetus for new directions in research on the association between CVD and 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. Manev H, Manev R. 5-lipoxygenase as a possible biological link between depressive symptoms and atherosclerosis. Arch Gen Psychiatry 2007;64:1333.
3. Rådmark O, Samuelsson B. 5-lipoxygenase: regulation and possible involvement in atherosclerosis. Prostaglandins Other Lipid Mediat 2007;83:162–74.
4. Chinnici CM, Yao Y, Praticò D. The 5-lipoxygenase enzymatic pathway in the mouse brain: young versus old. Neurobiol Aging 2007;28:1457–62.

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