Journal of the American College of Cardiology
© 2008 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 52, No. 17, 2008
ISSN 0735-1097/08/$34.00
doi:10.1016/j.jacc.2008.07.037

EDITORIAL COMMENT

The Complex Intersection of Inflammation and Oxidation

Implications for Atheroprotection*

Stephen J. Nicholls, MBBS, PhD, FRACP, FACC
Cleveland, Ohio

Therapeutic advances over the last 3 decades have made a dramatic impact on mortality from atherosclerotic cardiovascular disease. As a result, intensive modification of established risk factors has become increasingly integrated into guidelines designed to reduce cardiovascular risk. However, using existing therapies, event rates are reduced by no more than 40% in large randomized clinical trials. This observation suggests that residual risk will remain elevated despite an optimal use of currently available interventions. The expanding global burden of cardiovascular disease in association with obesity and associated metabolic risk factors is likely to further emphasize the need to develop new strategies to complement existing therapies.

See page 1370

Increasing evidence has focused on the role of inflammation and oxidation in the initiation and progression of atherosclerosis. The early stage of plaque development within the artery wall involves transudation and oxidation of low-density lipoprotein, with the accumulation of inflammatory cells and formation of foam cells. Elaboration of proinflammatory cytokines by foam cells promotes ongoing accumulation of cellular and necrotic material, features that are critical for progression and subsequent rupture of atherosclerotic plaque. As a result, there is considerable interest in these pathological cascades as targets for the development of new biomarkers for risk prediction and novel atheroprotective therapies. Given the prominent roles of both inflammation and oxidative stress in the setting of acute ischemic syndromes, it is has been proposed that such novel therapeutic interventions would be likely to have the greatest clinical benefit in the highest risk patients.

Despite increasing awareness of the role of these events in atherosclerosis, no new therapy specifically targeted at reducing either inflammation or oxidative stress in the artery wall has demonstrated clinical effectiveness in humans. In particular, the consistent failure of multivitamins to prevent cardiovascular events in large, randomized clinical trials has brought into question the concept that oxidation plays a major role in atherosclerosis (1). However, because no index of oxidative stress was quantified in these trials, it remains unknown whether these interventions had any impact on oxidation within the vessel wall. In addition, although it has been proposed that anti-inflammatory properties contribute to the clinical benefit of a range of established therapies, no agent that specifically targets vascular inflammation has shown a beneficial impact on cardiovascular risk in prospective clinical trials. As a result, it remains uncertain whether new agents, acting predominantly as antioxidant or anti-inflammatory agents, will have an impact on the residual risk of patients receiving established preventive therapies.

It seems likely that the most effective strategies will be those that directly modify established targets that can be easily quantified. Oxidized forms of low-density lipoprotein (OxLDL) have received considerable interest in the development of new biomarkers and therapies. OxLDL plays a pivotal role in foam cell formation and propagation of atherosclerosis. Circulating levels of antibodies against OxLDL are associated with reduced levels of surrogate markers of atherosclerosis (2). Immunization of oxidation epitopes evokes an antibody response and has been demonstrated to prevent lesion formation in animal models of atherosclerosis (3). Therefore, endogenous factors that promote induction of antibodies directed against OxLDL have the potential to prevent cardiovascular disease.

In this issue of the *Journal,* Sämpi et al. (4) report the relationship between systemic levels of interleukin (IL)-5 and antibodies to OxLDL in patients with subclinical atherosclerosis, as measured by carotid intimal-medial thickness. Investigation of 1,011 Finnish middle-aged subjects who participated in the OPERA (Oulu Project Elucidating Risk of Atherosclerosis) study revealed that increasing plasma levels of the cytokine IL-5 was associated with greater levels of antibodies binding to OxLDL and less subclinical atherosclerosis. This extends previous findings from murine models (5,6) and although these data do not establish a causal mechanistic link, they do suggest a potentially atheroprotective role for IL-5 via induction of antibodies against oxidized forms of low-density lipoprotein (LDL).

These observations further highlight the challenge of developing an effective approach to prevention of cardiovascular disease via protection of the vessel wall from the consequences of oxidative stress. Although many markers of oxidative stress have been reported in association with

*Editorials published in the *Journal of the American College of Cardiology* reflect the views of the authors and do not necessarily represent the views of *JACC* or the American College of Cardiology.

From the Departments of Cardiovascular Medicine and Cell Biology and the Center for Cardiovascular Diagnostics and Prevention, Cleveland Clinic, Cleveland, Ohio. Dr. Nicholls has received speaking honoraria from AstraZeneca, Pfizer, Takeda, and Merck Schering-Plough; consulting fees from AstraZeneca, Pfizer, Roche, Takeda, Merck Schering-Plough, and Novo Nordisk; and research support from LipoScience and AstraZeneca.

JACC Vol. 52, No. 17, 2008
October 21, 2008:1379–80

cardiovascular disease, it is likely that interventions that target those oxidative mediators that directly participate in disease propagation are more likely to be beneficial. The pivotal role played by OxLDL throughout the entire spectrum of stages of atherosclerosis therefore highlights its candidature as a factor of major interest. In a similar fashion, it is not surprising that given that myeloperoxidase (MPO) and its oxidant products promote atheroma formation and rupture, that systemic MPO levels independently predict clinical risk and that MPO inhibitors have received considerable interest as cardiovascular therapeutic agents (7).

The potential interaction between IL-5 and generation of antibodies directed against OxLDL also highlight the possibility that stimulation of endogenous antioxidant pathways may be beneficial. Even though many factors appear to possess antioxidant activities in vitro, this benefit is not always observed in the in vivo setting. It is likely that additional endogenous factors that specifically target oxidation of LDL may also protect the artery wall. Increasing evidence, for example, has highlighted the role of high-density lipoproteins in the prevention of LDL oxidation and inhibition of a number of pathways involved in generation of oxidative stress within the artery wall (8). Therefore, it is possible that a potential benefit of therapies that target high-density lipoproteins may be derived via stimulation of these endogenous antioxidant activities.

The findings by Sämpi et al. (4) have important implications for the development of strategies that target inflammatory and oxidative cascades. The observation that a potentially protective role of an inflammatory cytokine involves the reduction of 1 of the major oxidative mediators in the artery wall suggests that strategies that promote the activity of some inflammatory cytokines may, in fact, be protective. Furthermore, inhibition of these pathways in the course of treatment of inflammatory disease processes involving other organs may result in an unwanted detrimental impact on cardiovascular disease. As the potential impact of the crosstalk between inflammatory and oxidative pathways in atherosclerosis becomes further elucidated, the search to develop new therapies to reduce cardiovascular risk just got a little more complicated.

Reprint requests and correspondence: Dr. Stephen J. Nicholls, Department of Cardiovascular Medicine, Heart and Vascular Institute, Cleveland Clinic, Mail Code JJ-65, 9500 Euclid Avenue, Cleveland, Ohio 44195. E-mail: nichols1@ccf.org.

REFERENCES

1. Yusuf S, Dagenais G, Pogue J, Bosch J, Sleight P, on behalf of the Heart Outcomes Prevention Evaluation Study Investigators. Vitamin E supplementation and cardiovascular events in high-risk patients. N Engl J Med 2000;342:154–60.
2. Karvonen J, Päivänsalo M, Kesaniemi YA, Hörkkö S. Immunoglobulin M type of autoantibodies to oxidized low-density lipoprotein has an inverse relation to carotid artery atherosclerosis. Circulation 2003;108:2107–12.
3. Palinski W, Miller E, Witztum JL. Immunization of low density lipoprotein (LDL) receptor-deficient rabbits with homologous malondialdehyde-modified LDL reduces atherogenesis. Proc Natl Acad Sci U S A 1995;92:821–5.
4. Sämpi M, Ukkola O, Päivänsalo M, Kesäniemi YA, Binder CJ, Hörkkö S. Plasma interleukin-5 levels are related to antibodies binding to oxidized low-density lipoprotein and to decreased subclinical atherosclerosis. J Am Coll Cardiol 2008;52:1370–8.
5. Binder CJ, Hartvigsen K, Chang MK, et al. IL-5 links adaptive and natural immunity specific for epitopes of oxidized LDL and protects from atherosclerosis. J Clin Invest 2004;114:427–37.
6. Miller AM, Xu D, Asquith DL, et al. IL-33 reduces the development of atherosclerosis. J Exp Med 2008;205:339–46.
7. Nicholls SJ, Hazen SL. Myeloperoxidase and cardiovascular disease. Arterioscler Thromb Vasc Biol 2005;25:1102–11.
8. Barter PJ, Nicholls S, Rye KA, Anantharamaiah GM, Navab M, Fogelman AM. Antiinflammatory properties of HDL. Circ Res 2004;95:764–72.

Key Words: inflammation ■ oxidation ■ atherosclerosis ■ interleukin ■ oxidized low-density lipoprotein.