

## Statins for Atherosclerosis — As Good as It Gets?

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If ever there were a perfect marriage of drug with disease it might be between statins and atherosclerosis. At first the relationship was simple: statins inhibited synthesis of the cholesterol that contributed to atheroma, and less cholesterol meant less atheroma. Just as married couples often adapt to each other, so it is with statins and atheroma, or to be more precise, an increased understanding of their relationship has revealed an apparent adaptation. Atherosclerosis is now recognized to have a notable inflammatory component, and in parallel, statins appear to inhibit inflammatory processes directly. Rheumatologists pondering this phenomenon from the outside (and wondering whether they would eventually be asked to treat cardiovascular disease with immunosuppressive drugs) began to recognize distinct but related connections closer to home. Patients with rheumatoid arthritis and systemic lupus erythematosus (SLE) have a significantly increased risk of cardiovascular disease and therefore might benefit from statin therapy. The other side of the coin is the possibility that the antiinflammatory actions of statins can also improve the autoimmune aspect of the disease itself. Indeed, the list of disorders for which statins might prove beneficial is growing and now extends from multiple sclerosis and neurodegenerative disorders to rheumatoid arthritis and SLE.

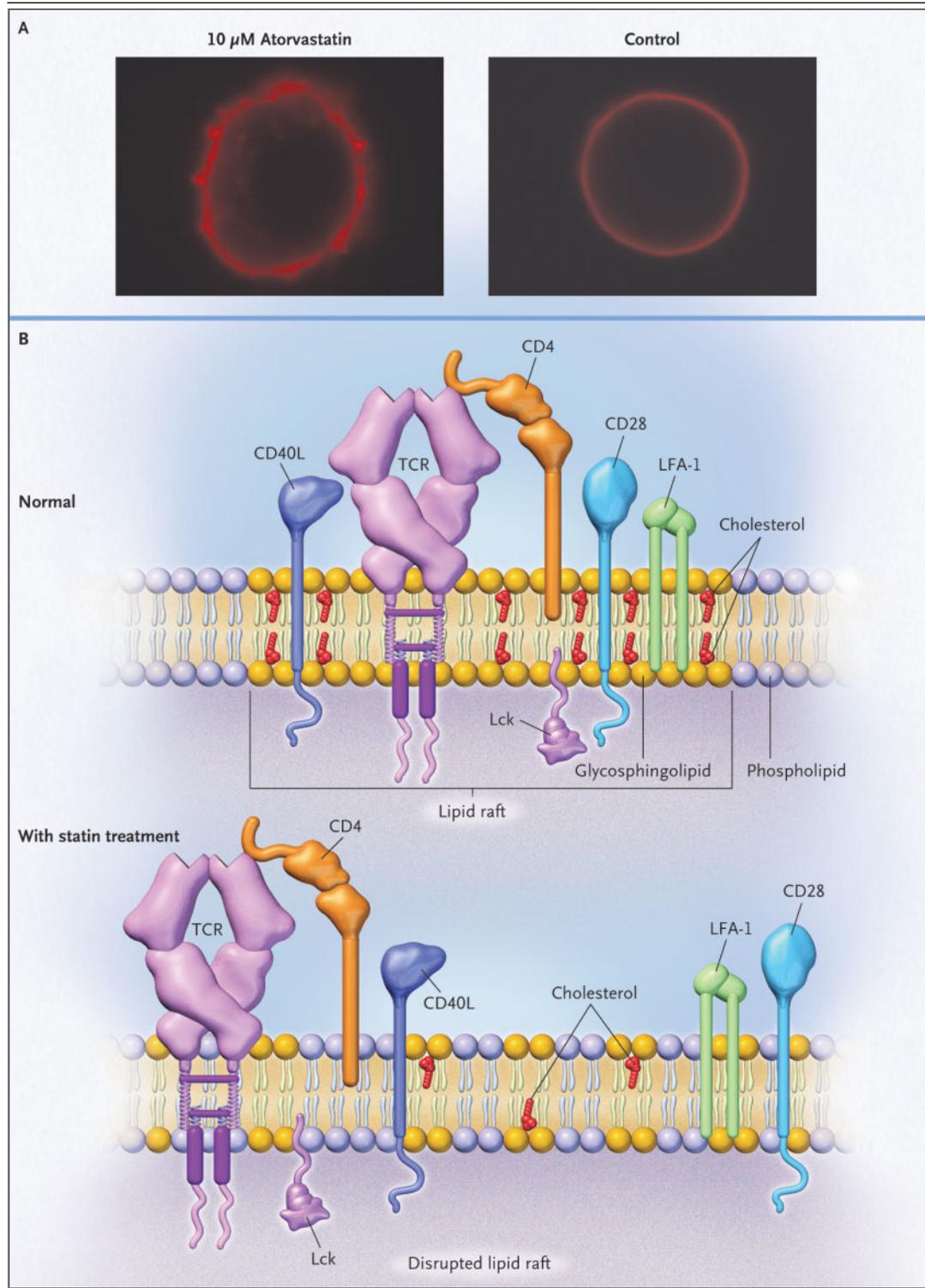
The action of statins turns out to be more complex and broader than was originally suspected, and recent studies have revealed their multiple immunologic actions. Among the first reports of the immunologic effects of statins was the finding that this class of drug inhibits the increase in cell-surface proteins of major histocompatibility complex class II induced by interferon- $\gamma$ .<sup>1</sup> Such proteins are central in presenting antigen and activating T cells, and their expression is often increased in inflammation. Increased production of interferon- $\gamma$  by activated T cells is characteristic of a number of autoimmune diseases in humans, including collagen-induced arthritis, and experimental autoimmune encephalomyelitis, a murine model of multiple sclerosis. Statin therapy proved effective in both these diseases as well as in murine lupus, in which the cytokine dysregulation is more complex but includes increased production of interferon- $\gamma$ .<sup>2</sup>

In fact, SLE provides an apt illustration of the

complex interaction among statins, atheroma, and the autoimmune disease itself. Interferon- $\gamma$  is now generally accepted as directly promoting atherosclerosis, and therefore, the increased production of interferon- $\gamma$  associated with active lupus would accelerate the formation of atheroma. Equally, there is now evidence from a murine model of lupus suggesting that elevated plasma cholesterol levels exacerbate SLE.<sup>3</sup> These results suggest that the use of statins could have several benefits for patients with SLE. Statin-induced reductions in cholesterol decrease atherosclerosis but may also ameliorate the disease itself. Moreover, statins mitigate autoimmunity, thereby opening the possibility of diminishing disease activity and, as a direct consequence, lowering the risk of atherosclerosis.

What about cardiovascular disease? The immunomodulatory effects of statins in various autoimmune diseases apply equally well to cardiovascular disease, in which surprisingly similar immune dysregulation is observed. Indeed, the inflammatory component of atherosclerosis, characterized by increased production of interferon- $\gamma$  by T cells, has led immunologists to suggest that atherosclerosis should be added to the list of organ-specific autoimmune diseases.

Two articles in this issue of the *Journal*, one by Nissen et al.<sup>4</sup> and one by Ridker et al.,<sup>5</sup> confirm that reducing the inflammatory component of cardiovascular disease through the use of statin therapy improves the clinical outcome independently of the reduction in serum cholesterol levels. Critical to the conclusions of both articles is the finding that a decrease in C-reactive protein, a marker of inflammation, is only weakly correlated with changes in serum lipid levels. However, from an immunologic perspective, the association between cholesterol levels and immunologic regulation may be closer than previously realized. Cholesterol is a key component of the structure and function of cell membranes. The response of lymphocytes to exogenous signals such as antigen is orchestrated by a number of molecules that cluster in cholesterol-rich areas of the cell membrane known as lipid rafts. Lipid rafts act as platforms, bringing together molecules essential for the activation of immune cells, but also separating such molecules when the conditions for activation are not appropriate. Several strands of



**Figure 1 (facing page). Effects of Statins on T-Cell Activation.**

Panel A shows Jurkat T cells that were incubated with 10  $\mu$ M atorvastatin or medium. The cells were then fixed with 4 percent paraformaldehyde and incubated with cholera toxin B, labeled with phycoerythrin. Cholera toxin B binds to glycosphingolipid GM1, which is a marker for lipid-raft domains. T cells exposed to atorvastatin show alterations in the expression and distribution of lipid-raft domains. In Panel B, the T-cell receptor (TCR) and costimulatory molecules, including lymphocyte function-associated antigen 1 (LFA-1), CD28, CD4, and CD40 ligand (CD40L), are recruited to lipid rafts after activation. Statins interfere with the activation of T cells by depleting membrane cholesterol and disrupting the integrity of lipid rafts. Statin treatment causes the exclusion from lipid microdomains of raft-associated molecules such as the Lck protein tyrosine kinase, the inhibition of actin polymerization, and the formation of a stable immunologic synapse and therefore disrupts T-cell activation.

evidence suggest that the inhibition of cholesterol synthesis by statins disrupts these lipid rafts and thereby influences the function of lymphocytes (Fig. 1).

Could all the immunomodulation by statins be ascribed to their ability to reduce cholesterol levels in the cell membrane? Serum and membrane cholesterol may be differentially affected by statin treatment, and only by assaying both could the full effects of statins be identified. Although the changes in membrane cholesterol levels may be relevant only at sites of lymphocyte activation, as in atheroma or

autoimmune diseases, the possibility that lymphocyte function may be generally impaired in the many patients who are taking statins raises a note of caution. However, even in the area of infection, there are suggestions that statin therapy has a favorable effect on sepsis and can reduce the replication of the human immunodeficiency virus.<sup>6</sup>

The notion that the antiinflammatory effects of statins ameliorate cardiovascular disease suggests that it should be possible to create other antiinflammatory agents, perhaps tailored to the specific immunologic abnormalities in atheroma. Determining the mechanisms of action of statins and their relative importance will help to rationalize the design of such therapies.

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## Bacterial Infections — A Major Cause of Death among Children in Africa

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For the past 25 years, since the United Nations Children's Fund (UNICEF) has been publishing estimates of mortality among children worldwide, the international medical community has been aware of the appalling burden of early deaths among African children. Early studies indicated that, in the absence of any effective medical care, children born in a rural African village had a probability of death before the age of five years of 30 to 50 percent.<sup>1</sup> From the outset, it was understood that many of these deaths result from the combined effect of poverty and malnutrition.<sup>2</sup> Since 1980, mortality rates have

fallen but remain high by global standards. Twelve African countries still report official death rates for children under the age of five of more than 20 percent. Community-based studies of death among children have been able to attribute these deaths to a number of common causes, either syndromes or specific diseases (Table 1).

These studies have suggested that the most important cause of death among children in Africa is malaria. The studies are based on the administration of a questionnaire in an interview with the family, conducted after the child's death, usually by a health