ISSN 0735-1097/03/$30.00
doi:10.1016/S0735-1097(03)00771-X

EDITORIAL COMMENT

Through the Looking Glass

An Angioscopic View of the Effect of Statin Therapy on Coronary Artery Plaques*

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Although there is no doubt that statins represent a marvelous advance in the prevention of cardiovascular disease, two observations indicate that the mechanisms of their beneficial effects are not yet fully understood. First, although it is well documented that statin therapy reduces death and acute myocardial infarction (MI) by more than 25%, angiographic studies have revealed that this benefit occurs with only a minor improvement in coronary artery stenosis (1). Second, whereas the lipid-lowering action of statins appears to account for much of their beneficial effect, in some studies, benefits have occurred that appear to be independent of lipid levels (2,3). The angioscopic findings provided by Takano et al. (4) in this issue of the *Journal* shine new light on the theories advanced to explain these paradoxes.

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The discrepancy between the substantial clinical benefit and persistent luminal stenosis has been attributed to "stabilization" of plaques (5) presumed to be vulnerable to disruption and thrombosis. However, there has been no reliable method to test this hypothesis in patients. The second discrepancy, the lack of a relation between the degree of lipid lowering and the benefits observed in a subset of studies, has been ascribed to positive actions of statins other than lipid-lowering. These "pleiotropic" effects, which might prevent cardiac events, include the ability to reduce inflammation, metalloproteinase activity, endothelial dysfunction, plaque thrombogenicity, and systemic coagulation tendency (6). Each of these actions is theoretically capable of blocking the complex pathophysiologic process leading from plaque formation to plaque disruption, and ultimately to cardiac events.

PATHOPHYSIOLOGY OF CORONARY EVENTS

Established facts. Many steps in the transition from asymptomatic atherosclerosis to the cardiac events of unstable angina, nonfatal MI, and sudden cardiac death are well understood. There is general agreement that these acute coronary syndromes most often result from disruption of a plaque that did not cause significant stenosis before the event. Such plaques, with a high risk of disruption, have been termed "vulnerable" plaques (7).

Although only limited prospective data are available, retrospective data indicate that the most common histologic type of vulnerable plaque is a lesion that has a large lipid pool, a thin cap, and an inflammatory infiltrate (8). Such thin-capped fibroatheromas have been referred to as TCFAs (9). The presence of proteolytic enzymes and positive remodeling has also been associated with vulnerability (10,11).

There are data to suggest that plaque disruption is often triggered by activities of patients, but it may also result from processes within the plaque (12). In many cases, the disruption produces only a minor mural thrombosis, which then organizes without causing ischemia or producing symptoms. Numerous factors may affect the likelihood that a plaque's rupture will lead to unstable angina or a more serious cardiac event. If the thrombotic stimulus of the disrupted plaque is high, the rheology favorable, and the systemic clotting tendency increased, the thrombus may become occlusive (13). If the lesion is located in a large vessel without sufficient collaterals, and if increased vasoconstrictor tone is present, the occlusion may produce myocardial ischemia. Limited and transient ischemia may produce only unstable angina, whereas more severe and permanent ischemia leads to MI. Ischemia may produce sudden cardiac death directly by causing an arrhythmia, or indirectly, through the results of a MI. Sudden death may be more likely if the myocardium is vulnerable to arrhythmias.

Areas of uncertainty. Despite this considerable understanding of pathophysiology, questions remain about processes related to the plaque, ischemia, and cardiac events of infarction and sudden death.

The distribution of vulnerability to disruption within the coronary arteries is not known. Because atherosclerosis is a systemic disease, and systemic markers of inflammation predict coronary events (14), it can be argued that vulnerability is a diffuse process that will not benefit from local diagnosis or local therapy. Alternatively, because patients generally experience difficulty at only a single spot in an artery, it can be argued that vulnerability is, in many cases, focal. Recent data on the presence of multiple disrupted plaques in some patients with an acute coronary syndrome suggest that in these cases, vulnerability was at least multifocal (15).

If it is assumed that vulnerability is focal or even multifocal, then it is of value to further characterize the tissue types that lead to vulnerability. The inflamed TCFA is generally considered to be the most common type of vulnerable plaque and other, less common subtypes have been identified. As the histologic subtypes are characterized further through autopsy studies, it will be necessary to determine if such sites can be identified in advance of their

*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.

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JACC Vol. 42, No. 4, 2003
August 20, 2003:687–9

rupture. If so, this would make it possible to create a much-needed index of vulnerability for plaque disruption.

The vulnerable patient. Although it is certain, on the basis of autopsy findings, that plaque disruption does not always lead to symptoms (16), the frequency of asymptomatic plaque disruption in living patients is not known. For each disruption that leads to symptoms, it has been estimated that as many as 10 asymptomatic disruptions occur. Improved knowledge of the factors leading from a vulnerable plaque to disruption, and then to unstable angina, MI, and sudden cardiac death would enhance efforts to develop an *index of vulnerability for a cardiac event*—a means to identify *the vulnerable patient*. Such an index will likely prove to be more useful than a plaque disruption index as a guide for clinical interventions.

CONTRIBUTION OF ANGIOSCOPY

Coronary angioscopy is an excellent research tool with which to approach the unanswered questions regarding plaque vulnerability, plaque disruption, and the effect of treatment in living patients. In contrast to angiography, which provides little information beyond the degree of stenosis a coronary plaque is causing, angioscopy provides an excellent view of the color and luminal surface features of plaques. Autopsy correlation studies have established that fibrotic plaques are white, plaques with lipid pools are yellow, and that more intense shades of yellow are associated with thinner caps. Angioscopy is an extremely sensitive detector of thrombus and intimal surface irregularities, which makes it an excellent method for identification of disrupted plaques. Several studies, which require confirmation, suggest that yellow plaque color predicts plaque disruption and clinical events (17–20). The major limitation of the technique is that it requires coronary artery occlusion and removal of blood from the field of view.

The study by Takano et al. (4) reported in this issue of the *Journal* utilizes this powerful research tool to assess possible coronary plaque stabilization by statin therapy. The authors report that 12 months of therapy with atorvastatin reduced the yellow score of plaques and reduced signs of plaque disruption compared with the results observed in a nonrandomized comparison group. The decrease in plaque color correlated with the decrease in low-density lipoprotein (LDL), whereas there was no correlation between the decrease in disrupted score and the decrease in LDL.

Several methodologic issues need to be considered before interpreting the results of this study. The study was not randomized or fully blinded, and the end point, the intensity of color by visual inspection, is subjective. The lack of random assignment to statin therapy raises questions about the comparability of the groups and similarity of end point acquisition methods. Although the groups are matched for several variables, the study results may be confounded by uneven distribution of additional unidentified baseline variables related to the study outcomes. Further, although the image analysis was blinded, biased image acquisition could have occurred because the intensity of the light was adjusted for each patient. If a stronger light were used at follow-up in the atorvastatin cases, the plaques might incorrectly appear to be whiter in the treated group (21,22).

For the sake of discussion, let us assume that these limitations did not compromise the validity of the study, and that similar results would be obtained in a confirmatory study. The decrease in the yellow score with atorvastatin therapy and the direct correlation of that decrease with the degree of LDL lowering presumably reflect a decrease in the lipid content of plaques and/or an increase in thickness of the caps overlying lipid pools—changes that would be expected to stabilize the plaque. This beneficial histologic change has also been suggested in a trial of statin therapy in which measurements were made with intravascular ultrasound. In the statin-treated group, the echogenicity of the plaques increased after lipid lowering, suggesting the conversion of lipid-rich plaques to a more stable fibrous composition (23).

Histologic documentation of such changes has been obtained in an animal model, in which nonhuman primates were transferred from an atherogenic to a nonatherogenic diet. Although similar histologic data from coronary patients are not available, changes with therapy have been examined in carotid artery endarterectomy specimens. Pravastatin therapy enhanced the collagen content and decreased the lipid content of carotid plaques. In aggregate, these studies and the findings of the present study make it quite likely that atorvastatin therapy decreased the lipid content and/or increased cap thickness in these patients, changes expected to stabilize plaques.

Support for the conclusion that the plaques were stabilized is provided by the second observation of Takano et al. (4) that, in the atorvastatin-treated group, the disruption score (an index of thrombosis and/or intimal disruption) was also decreased. In contrast to the findings for lipid-related yellow score, this change was not correlated with the change in LDL level.

It may be that the lack of correlation is due to the relatively small sample size. However, it is also possible that the atorvastatin therapy prevented plaque disruption by other effects in addition to LDL lowering. The pleiotropic effects of statin may well be additional contributors to enhanced cap integrity and reduced thrombosis. This finding is in accord with clinical studies in which the decrease in events produced by statin therapy is not consistently correlated with the change in LDL levels.

Both the decrease in yellow score and the decrease in disruption score are signs of plaque stabilization by a statin that could explain the apparent paradox discussed earlier, that the clinical benefits of statin therapy exceed their effects on coronary stenosis (1).

FUTURE USE OF ANGIOSCOPY

This study clearly demonstrates the ability of angioscopy, as a research tool, to contribute to our understanding of events

within the coronary arteries of living patients. As was this study, the majority of the valuable angioscopy studies have been performed in Japan. Perhaps these intriguing results will increase the use of angioscopy in the U.S. and other countries where it is an underutilized research tool.

In the near term, it would be extremely useful if an attempt could be made to replicate the findings of Takano et al. (4) in a randomized trial. Studies in larger numbers of patients will be needed to confirm the reported findings of other studies indicating that yellow plaques are more likely to cause clinical events than are white plaques. Testing of this linkage would be an important contribution to the debate as to whether there are discrete locations in a coronary artery, which can be identified prospectively, that have an increased likelihood of causing an event.

Despite its utility as a research tool for use in specialized centers, angioscopy is not well suited for use in multicenter studies, and certainly is not a desirable tool for clinical use, because it requires a blood-free field. However, it may be possible to use angioscopy as a standard for validation of other intravascular techniques to detect vulnerable plaque (such as thermography) (24), that do not require coronary occlusion

These less demanding techniques, perhaps together with angioscopy itself, should be compared to determine the best method to identify foci of vulnerability to disruption. If such foci exist, and can be detected, the device could then be used to select high-risk patients for enrollment in trials of therapy. In a trial of local treatment, which might be possible with drug-eluting stents, photodynamic agents, or other measures, the device would indicate the site in need of therapy. In a trial of systemic treatment, perhaps with extreme lipid lowering, the method could be used to obtain a follow-up measurement, as was done in the present study, to evaluate the effect of therapy on an index of vulnerability that can be attained with smaller numbers of patients than would be required for a clinical end point.

Although the potential benefits of vulnerable plaque detection and treatment are massive, at present, there are insufficient data to recommend routine clinical attempts to detect or treat such lesions. Clinical studies in large numbers of patients must first demonstrate that detection and treatment of vulnerable plaques reduces cardiac events. Detection and treatment must also be shown to be cost-effective. Angioscopy may contribute to such trials, or at least to the development of less complex detection techniques for use in such trials, as indicated by the important findings of Takano et al. (4).

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