Lipid Lowering and Plaque Regression

New Insights Into Prevention of Plaque Disruption and Clinical Events in Coronary Disease

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Treatments designed to favorably affect the clinical impact of coronary artery disease (CAD) have two fundamental goals. The first goal is to diminish the symptomatic limitations imposed by arterial obstructive disease, in which the vessel’s capacity to fully meet the varying oxygen demands of the myocardium is impaired. Vascular capacity may be abnormal because of a fixed flow-limiting coronary stenosis,1,2 abnormal epicardial vessel tone,3,4 intermittent arterial vasospasm,5 microvascular dysfunction,6,7 or inadequate collateral development. A variety of medical approaches are now used to palliate symptoms by favorably altering the oxygen supply–demand imbalance. Alternatively, this first goal of symptom relief may be achieved through more direct structural and/or physiological changes that favorably affect the diminished vascular flow capacity. These include relaxation of excess vasoconstrictor tone, development of collateral vessels, or reduction in the severity of flow-limiting stenosis (“regression”). The latter has been questioned as a possible mechanism for symptom relief. In this report, the data supporting the occurrence of regression and its mechanisms are reviewed, together with the role of lipid lowering in achieving it.

The second fundamental goal of therapy in CAD is to prevent the anticipated worsening of symptoms or progression to a clinical event such as sudden death, myocardial infarction, or worsening angina requiring bypass surgery or angioplasty. In this report, the mechanisms of gradually progressive arterial obstruction are discussed together with the mechanisms of plaque disruption resulting in abrupt worsening of arterial obstruction. Data presented indicate a linkage between lipid lowering and stabilization of the plaque structure. This set of observations supports the hypothesis that lipid-lowering therapy prevents clinical events by selectively depleting of lipids, or “regressing,” a relatively small subgroup of lipid-rich plaques that are predisposed to plaque fissuring, ulceration, and hemorrhage and that account for the great majority of clinical events.

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Promoting Regression

Our understanding of atherosclerosis regression comes largely from animal experiments and from human arteriographic studies. There are important biological differences between the various experimental models of atherosclerosis and the disease in humans, and there are important differences in the methods for assessing disease. As a result, concepts emerging from these two perspectives are not always comparable. Even the basic term regression means something quite different to the experimental pathologist than to the clinician, as can be seen in the histological sections of Figure 1. To the former, regression means shrinkage of intimal plaque through a reduction in its major components: smooth muscle, macrophages, connective tissues, and lipid. To the clinician interpreting human disease in terms of its arteriographic appearance, regression is defined as an increase in the diameter of the narrowed arterial lumen; such improvement occurs infrequently in the natural course of the disease. This “luminal” definition of regression encompasses the effects of plaque shrinkage but also of a variety of other possible mechanisms. For example, lysis of fully occlusive thrombi or of mural thrombi is commonly seen in the course of unstable clinical syndromes.8,9 Healing may favorably remodel an acutely disrupted plaque.10 Physiological remodeling of the underlying vascular architecture can improve arteriographic lumen size independently of changes in plaque size.11-13 Relaxation of arterial vaso-motor tone can similarly increase lumen size.3,4 The role of the endothelium and the relation of therapy to its function are proving to be important in many of these processes.4,7,12,14-17 By their nature, these arteriographic images do not permit an easy distinction among the possible mechanisms of regression. Thus, the important question is not, “does arteriographic regression happen in patients?” (it does), but rather, “can we promote such regression with a magnitude and frequency sufficiently great to justify a major therapeutic strategy?” Important related questions are, by which of the above mechanisms is regression achieved?; does such induced regression provide clinical benefits?; and, if so, by what means? Although there is no consensus regarding these questions, encouraging evidence is emerging.

Experimental Observations

Convincing evidence that atherosclerosis can regress with lipid lowering has come from the nonhuman pri-
mate studies of Wissler et al.,18 Armstrong and Megan,19,20 Clarkson et al.,21 and Small et al.,22 In the typical experimental regression trial, atherosclerosis is induced, often by cholesterol feeding, in a group of animals. Severity and composition of intimal disease is subsequently assessed at specified times, with group-averaged chemical and histological end points. After prolonged exposure to a cholesterol-rich “atherogenic” diet, plasma lipids increase to >600 mg/dL, and there are large increases in coronary artery collagen (threefold), elastin (fourfold), and cholesterol (sevenfold, mostly esterified). When the animals are changed to a vegetarian “regression” diet, plasma lipids fall quickly to normal (140 mg/dL), and the arterial lipid and connective tissue changes partially regress over 20–40 months. Collagen does not decrease much from its peak value (~20%), but elastin (~50%) and cholesterol (~60%) do,20,21 and there is a fibrous transformation of the myointimal cellular response.23 Not all forms of cholesterol are easily depleted from these cholesterol-rich intimal lesions. The more mobile forms, including cholesteryl esters in foam cells, lipoproteins, and cholesteryl ester droplets, have been shown to regress; but the cholesterol monohydrate crystals of the core lipid region are resistant to mobilization.22,23 Histological measurements show that plaque size is reduced during regression therapy.19,22,24

Evidence in Humans
As late as 1987, clinical regression was an uncertain entity. Only anecdotal evidence suggested that the animal observations could be extended to patients with atherosclerotic disease. Kuo et al.,25 Brensike et al.,26 Duffield et al.,27 Nash et al.,28 and Nikkila29 had pio-
neered the use of arteriographic trials; in general, they concluded that lipid-lowering therapy reduced the frequency of progression. In these studies, however, regression of disease was rarely observed and was not found to be increased by the therapies tested. A more recent series of randomized clinical arteriographic trials beginning with the National Heart, Lung, and Blood Institute (NHLBI) Type II Coronary Intervention Study (1984) has provided a perspective on the magnitude and frequency of regression and conditions under which it can occur in our patients. These studies and their lipid response data are summarized in Table 1. Their results, based on arteriographic and clinical end points, are summarized in Table 2. In order of their publication, they are 1) NHLBI Type II: a 5-year comparison of diet versus diet plus cholestyramine among patients selected for >90th percentile LDL cholesterol and some evidence for coronary disease;26 2) CLAS: The Cholesterol-Lowering Atherosclerosis Study compared diet with diet plus niacin and colestipol for 2 years among male, post–coronary bypass patients;30 3) POSCH: The Program of Surgical Control of the Hyperlipidemias was a 9.7-year mean follow-up of patients with cholesterol >220 mg/dL who survived a first myocardial infarction and who were randomly assigned either to partial ileal bypass or to medical management in a “usual care” strategy;31 4) Lifestyle: The Lifestyle Heart Trial compared usual care with a variety of hygienic changes including a very-low-fat vegetarian diet plus moderate exercise and relaxation techniques among patients with clinically manifest coronary disease;32 5) FATS: The Familial Atherosclerosis Treatment Study compared a moderate approach to lipid lowering with two more intensive drug regimens.
TABLE 1. Summary Descriptions for Nine Reported Arteriographic Lipid-Lowering Trials: Lipid Response to Treatments

<table>
<thead>
<tr>
<th>Study*</th>
<th>n</th>
<th>Entry requirements</th>
<th>Control regimen†</th>
<th>Regimen</th>
<th>LDL</th>
<th>HDL</th>
<th>Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>NHLBI II</td>
<td>143</td>
<td>CAD, LDL</td>
<td>D</td>
<td>D+R</td>
<td>−31%</td>
<td>+8%</td>
<td>5</td>
</tr>
<tr>
<td>CLAS I</td>
<td>188</td>
<td>CAGB</td>
<td>D(−)</td>
<td>D+R+N</td>
<td>−43%</td>
<td>+37%</td>
<td>2</td>
</tr>
<tr>
<td>POSCH</td>
<td>838</td>
<td>MI, CHOL</td>
<td>D</td>
<td>D+PIB±R</td>
<td>−42%</td>
<td>+5%</td>
<td>9.7</td>
</tr>
<tr>
<td>Lifestyle</td>
<td>48</td>
<td>CAD</td>
<td>U</td>
<td>V+M+E</td>
<td>−37%</td>
<td>−3%</td>
<td>1</td>
</tr>
<tr>
<td>FATS (N+C)</td>
<td>146</td>
<td>CAD, Apo B</td>
<td>D±R</td>
<td>D+R+N</td>
<td>−32%</td>
<td>+43%</td>
<td>2.5</td>
</tr>
<tr>
<td>FATS (L+C)</td>
<td>138</td>
<td>CAGB</td>
<td>D</td>
<td>D+R+L</td>
<td>−46%</td>
<td>+15%</td>
<td>2.5</td>
</tr>
<tr>
<td>CLAS II</td>
<td>97</td>
<td>FH</td>
<td>U</td>
<td>D+R+N±L</td>
<td>−39%</td>
<td>+25%</td>
<td>2</td>
</tr>
<tr>
<td>UC-SCOR</td>
<td>300</td>
<td>CAD, CHOL</td>
<td>U</td>
<td>D+(R/N/L/F)+E, BP</td>
<td>−21%</td>
<td>+13%</td>
<td>4</td>
</tr>
<tr>
<td>STARS (D)</td>
<td>113</td>
<td>CAD</td>
<td>U</td>
<td>D</td>
<td>−16%</td>
<td>0%</td>
<td>3</td>
</tr>
<tr>
<td>STARS (D+R)</td>
<td>14</td>
<td>CAD, CHOL</td>
<td>U</td>
<td>D+R</td>
<td>−36%</td>
<td>−4%</td>
<td>3</td>
</tr>
</tbody>
</table>

LDL, low density lipoprotein >90th percentile; HDL, high density lipoprotein; N, nicotinic acid; C, colestipol; L, lovastatin; D, diet; R, resin (colestipol or cholestyramine); CAD, coronary artery disease; CAGB, coronary artery bypass graft surgery; MI, myocardial infarction; CHOL, cholesterol >220 mg/dL; apo B, apolipoprotein B ≤125 mg/dL; FH, familial hypercholesterolemia; U, usual care; PIB, partial ileal bypass; V, vegetarian diet <10% fat; M, relaxation techniques; E, exercise program; F, fibrate-type drugs; BP, blood pressure therapy.

*See text for details and full name of the studies. †Mean LDL cholesterol response to control regimen, −7%; mean HDL cholesterol response, 0%.

among men with elevated apolipoprotein B (≥125 mg/dL) and coronary disease; 6) CLAS II: an extension of the CLAS trial to 4 years among about three fourths of the original participants; 7) UC-SCOR: The University of California San Francisco investigators, as part of their Atherosclerosis SCOR Program Project, compared usual care with combined diet, colestipol, niacin, and possibly lovastatin among men and women selected for the genetic disorder familial hypercholesterolemia. Coronary disease was rarely clinically manifest among these severely hyperlipidemic subjects; 8) STARS: The St. Thomas Atherosclerosis Regression Study compared usual care with dietary counseling or with diet plus cholestyramine among male patients with coronary disease and with cholesterol >220 mg/dL; 9) SCRIP: The Stanford Coronary Risk Intervention Project studied patients with clinically established coronary disease. The usual care control group was compared with those given a risk reduction regimen targeted at hyperlipidemia, hypertension, obesity, and cigarette use and including dietary counseling plus a structured exercise program; and 10) Heidelberg: In this study, regular programmed physical exercise plus an American Heart Association phase 3 diet is compared with the usual care.

TABLE 2. Summary of Arteriographic Outcomes and Frequencies of Reported Clinical Events in Nine Lipid-Lowering Trials

<table>
<thead>
<tr>
<th>Study*</th>
<th>Control patients</th>
<th>Treatment patients</th>
<th>% “Event”‡ reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>NHLBI</td>
<td>Progression (%)</td>
<td>Regression (%)</td>
<td>∆(%)†</td>
</tr>
<tr>
<td>CLAS</td>
<td>9</td>
<td>7</td>
<td>...</td>
</tr>
<tr>
<td>POSCH (5 years)</td>
<td>65</td>
<td>6</td>
<td>...</td>
</tr>
<tr>
<td>Lifestyle</td>
<td>32</td>
<td>32</td>
<td>+3.4</td>
</tr>
<tr>
<td>FATS (N+C)</td>
<td>46</td>
<td>11</td>
<td>+2.1</td>
</tr>
<tr>
<td>FATS (L+C)</td>
<td>14</td>
<td>18</td>
<td>...</td>
</tr>
<tr>
<td>CLAS II</td>
<td>83</td>
<td>6</td>
<td>...</td>
</tr>
<tr>
<td>UC-SCOR</td>
<td>41</td>
<td>13</td>
<td>+0.8</td>
</tr>
<tr>
<td>STARS (D)</td>
<td>46</td>
<td>4</td>
<td>+5.8</td>
</tr>
<tr>
<td>STARS (D+R)</td>
<td>...</td>
<td>10</td>
<td>...</td>
</tr>
<tr>
<td>SCRIP</td>
<td>42</td>
<td>4</td>
<td>+3.0</td>
</tr>
<tr>
<td>Heidelberg</td>
<td>53</td>
<td>8</td>
<td>...</td>
</tr>
</tbody>
</table>

N, nicotinic acid; C, colestipol; L, lovastatin; D, diet; R, resin (colestipol or cholestyramine).

*See text for the details, abbreviations, and full name of these studies. †∆(%) is usually reported as the average change in percent stenosis over all the lesions measured per patient. A positive (+) value represents “progression”; (−), “regression”. ‡Events are variably defined in these studies; in general, the frequency of cardiovascular events (death, myocardial infarction, unstable ischemia requiring revascularization) in control and treated groups are compared using the sometimes sketchy details and definitions provided. §Statistical comparison uses a lesion-based method. ||Studies for which the reduction in cardiovascular clinical events was statistically significant.

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approach among 113 men routinely catheterized for stable angina pectoris.\textsuperscript{38} In the NHLBI II, CLAS, CLAS II, and POSCH trials, disease progression was assessed visually by panels of experts blinded to patient identity, randomization, and temporal sequence of the film pair. In the remainder, a similarly blinded analysis incorporated techniques of computer-assisted quantitative coronary arteriography (QCA).\textsuperscript{39} Of interest, in only five of these nine trials was there an entry requirement for even modest hyperlipidemia. Despite the diversity among these studies in clinical presentation, lipid entry requirements, treatment regimens, and methods for arteriographic analysis, the outcomes, summarized in Table 2, are surprisingly consistent. Each study demonstrated a benefit from treatment, whether by diet, by diet supplemented by other lifestyle changes, or by lipid-altering drugs. As a generalization of the composite of results, 8\% of the control group patients were judged to have improvement in arterial obstruction ("regression") during the study period. By contrast, about one fourth of treated patients were found to have improved (a threefold increase). An example of this type of comparison, using FATS results, is provided in Figure 2. As seen in Table 2, averaged estimates of disease severity per patient worsened (progressed) by about 3\% stenosis among the control subjects, whereas they improved (regressed) by 1\%–2\% stenosis among the treated patients.

When these results are expressed in terms of absolute change in arterial narrowing, they appear to be remarkably small. In FATS, for example, the minimum lumen diameter of control group lesions progressively narrowed by a per-patient average of \(-0.050\) mm over 2.5 years, whereas treated group lesions improved by \(+0.024\) (\(p<0.01\)), for a treatment-induced difference of \(0.074\) mm (less than 0.1 mm!). Similarly, this difference was \(0.096\) mm (\(p<0.01\)) in SCRIP, \(0.13\) mm (\(p<0.05\)) in Heidelberg, and \(0.35\) mm (\(p<0.003\)) in STARS. These treatment effects achieve statistical significance because the group variance of this estimate of disease change is also quite small—a testament to the precision of the QCA methods. In nearly every study, the frequency of clinical cardiovascular events was reduced substantially, although the reductions achieved statistical significance in only three. Failure to confirm a clinical benefit is not unexpected, since the sample size required for trials using arteriographic end points is much smaller than for trials using clinical end points.

Figure 3 provides examples of regression occurring in intensively treated FATS patients over a 2.5-year period. As these images suggest and the data of Figure 4 confirm, regression may occur in mild, moderate, and severe lesions. Although regression was more likely to occur among the more severe lesions, the relative benefit from therapy was roughly uniform over the spectrum of disease severity. Those lesions that did regress improved by an average \(\pm\)SD of \(19\%\pm12\%\) stenosis and, after 12 cases of recanalization from 100\% stenosis were excluded, by \(16\%\pm5\%\) stenosis. Thus, very few lesions (about 5\%) undergo natural, or spontaneous, regression by the criterion amount of \(\leq10\%\) stenosis. Although this number can be significantly increased (to about 12\%) by lipid-lowering therapy, a large majority of stenoses do not improve even with "intensive" regimens that result in marked alterations in the lipid and lipoprotein profile. Yet, these regimens are commonly associated with much more substantial reductions in clinical event rate (Table 2). We will return later to this apparent paradox.

The impulse to "meta-analyze" these trials is, we believe, likely to result in erroneous conclusions. First, the interventions are not all of a single class. Second, patient selection criteria and study durations vary widely. Third, the angiographic assessment ranges from visual scoring to QCA. Even among the studies using QCA, there is a threefold variation in the number of lesions measured per patient. This seemingly innocent difference actually introduces a substantial methodological bias. When a small number of lesions are selected in a given patient, they are usually the most severe ones seen; as a consequence, the mean severity of "all lesions measured" is relatively great. Conversely, when a larger number of lesions is measured per patient, their mean severity is usually less. For example, in FATS, a mean of 8.6 proximal lesions was measured per patient; mean baseline severity of these lesions averaged 33\%. In the Lifestyle Trial, these numbers were 4.8 lesions per patient and 41\% stenosis, and in the Heidelberg Trial, 3.1 lesions per patient and 64\% stenosis. As Figure 4 indicates, moderate and severe stenoses (\(\geq40\%\) stenosis), taken together, are more likely to progress with the control regimen and to regress with intensive therapy than are the milder lesions. As a predictable result, the treatment benefit will appear larger in studies in which a small number of more severe lesions is measured per patient. Indeed, this has been the case. In FATS, Lifestyle, and Heidelberg, for example, the annualized change in stenosis severity differs between control and treatment groups by 1.2\%, 5.6\%, and 4.0\% stenosis per year, respectively (Tables 1 and 2). We believe these differences between studies are artifacts of the methodology rather than true differences in therapeutic efficacy. We conclude that they cannot be compared directly, except perhaps in terms of the effect of therapy on the ratio of progression/regression.
Preventing Progression

Pathological Processes

This review focuses briefly on several clinically important aspects of plaque biology: lipid accumulation in the foam cells and core region, plaque fissures and their healing, and vasoconstrictor tone.

Low density lipoprotein (LDL) and, more recently, lipoprotein(a) [Lp(a)] have been demonstrated in the intimal extracellular space, the cholesterol content of which has been shown to originate from plasma LDL cholesterol. Lipid may also accumulate in the intima in subendothelial monocyte-derived macrophages. Such “foam cell” formation is thought to occur by unregulated scavenger receptor uptake of oxidized LDL and possibly of Lp(a). Foam cells are abundant in precursor fatty streak lesions and in the shoulders, cap, and basilar neovascular complex of advanced plaques. Lipid may enter the core region of the fibrous plaque by transmural flux of its more mobile forms (lipoprotein particles, droplets, and vesicles), or it may be deposited there during foam cell necrosis. In the core region, lipids coalesce into lower-energy phases dictated by the local cholesterol, phospholipid, and cholesteryl ester concentrations. Droplet and vesicular forms of the latter and cholesterol monohydrate crystals are the dominant core lipids. Although transmural flux of small peripherally lipid droplets has been thought to initiate core lipid accumulation in the earliest human aortic lesions, the contribution of foam cell necrosis to the continued accumulation of core lipid in the larger mature fibrous plaques remains to be determined. This question is important because of the possible therapeutic role of antioxidants, which, by preventing LDL oxidation, may act to prevent foam cell formation and, ultimately, core lipid accumulation.

As described below, the fissuring of plaques is now recognized as the key event triggering abrupt arterial occlusion and ischemia. Also, “silent” fissuring can occur in the absence of clinical symptoms, suggesting another mechanism of plaque growth. Mural thrombus, or that formed at sites of intraplaque hemorrhage, can undergo a fibrous transformation caused by ingrowth and organization by smooth muscle cells, thus expanding the plaque connective tissue mass. Evidence supporting this proposed mechanism of fibrogenesis is detailed elsewhere.

Increased vasoconstrictor tone worsens arterial narrowing and contributes to progressive obstruction. Atherosclerosis affects vascular tone by interfering with the normal function of the endogenous vasodilator, endothelium-derived relaxing factor (EDRF), which is nitric oxide or an analogue. This appears to account for the apparently paradoxical epicardial coronary vasoconstrictor effects of isometric and aerobic exercise in patients with CAD. Since the impairment of function is experimentally reversed by reducing dietary
cholesterol despite persistence of intimal thickening and since vascular smooth muscle cell responsiveness to direct dilators is largely unaltered by atherosclerosis, it is felt that vasorelaxant dysfunction is caused by a direct effect of the atherogenic state on the endothelial release of EDHF. The mechanism of impairment is unknown, but LDL cholesterol and, more specifically, oxidized LDL have been implicated.

Evidence in Humans

Support for the idea that lipid-lowering therapy can effectively retard progression of atherosclerotic arterial obstruction in patients dates to 1979. The composite of such evidence from randomized arteriographic trials is summarized in Table 2. Again, despite the diversity of these trials, the evidence for reduced lesion progression is surprisingly consistent. Approximately one half of the control group patients in Table 2 were judged to have worsening arterial obstruction during the study period. By contrast, about one fourth of the treated patients worsened (a 50% reduction from control values). Again, the example of Figure 2 illustrates this comparison, using FATS data.

Figure 4 demonstrates that the likelihood of a lesion's progression is, in part, determined by its baseline severity. Intensive lipid-lowering therapy decreases, by about fourfold, the likelihood of definite lesion progression among mild and moderate lesions but does not appear to reduce the chance of progression of the small number of severe lesions studied.

Preventing Plaque Disruption and Clinical Events

The landmark Lipid Research Clinics–Coronary Primary Prevention Trial established that significant reduction of clinical coronary events but not of cardiac or total mortality occurred in association with a 9% reduction, relative to the dietary control, in total cholesterol and a 13% reduction in LDL cholesterol achieved with diet and cholestyramine. Importantly, the magnitude of cardiovascular benefit correlated in a subgroup analysis with the degree of total and of LDL cholesterol reduction. The Helsinki Heart Trial also achieved a significant reduction in total cardiac events but not mortality. And the 15-year follow-up of the Coronary Drug project showed highly significant (11%) reductions in cardiac and all-cause mortality only in the niacin-treated group.

Additional evidence that clinical events are decreased by lipid-lowering therapy is presented in Table 2. Each trial reports events somewhat differently. In general, when reported, we have classified as clinical events cardiac death, confirmed myocardial infarction, and progressive or unstable ischemia requiring revascularization. The data from FATS in Table 2 demonstrate a 70–80% reduction from control values in event rate. It is clear from Table 2 and from the primary prevention trials that clinical cardiovascular events are reduced by lipid-lowering therapy. It is of interest that clinical benefits were statistically significant only in trials with an entry requirement for lipid elevation. Indeed, the amount of risk reduction seems out of keeping with the average 1–2% stenosis regression in lesion severity and with the fact that only about 12% of all intensively treated lesions actually regress. How can regression of a small number of lesions result in a 70–80% reduction in the frequency of clinical events? To understand how, we must understand the series of events in the plaque that turn a stable quiescent lesion into an unstable culprit lesion precipitating a clinical event.

Determinants of Plaque Disruption

Acute ischemic syndromes are most commonly precipitated when mild or moderate coronary lesions become disruptively transformed into severely obstructive culprit lesions. Such disruption usually involves fissuring of the fibrous cap of the atheroma, often with intramural hemorrhage and mural or occlusive thrombus. The plaque at high risk for such fissuring has a large core lipid pool and a structurally weakened fibrous cap. The cap can be weakened by the exudate or death of its smooth muscle cells, by an accumulation of lipid-laden macrophages, or by proteolytic or mechanical degradation of its collagen. Several evolving insights have greatly altered our understanding of the precipitation of plaque events leading to acute coronary events.

First, mild and moderate coronary lesions (<70% stenosis) may abruptly progress to severe obstruction, with resulting unstable angina, myocardial infarction, or...
death. In fact, a majority of clinical events occur under these circumstances.\textsuperscript{8,71} Among patients undergoing thrombolytic therapy for acute myocardial infarction, the severity of the atherosclerotic stenosis underlying the thrombotic occlusion was measured at <50\% diameter stenosis in one third of cases and between 50\% and 60\% stenosis in another third.\textsuperscript{8} From another perspective, when the lesion precipitating a myocardial infarction has, by chance, been seen on a recent angiogram, its preinfarct severity averages 50\% stenosis, and it will not usually possess visible features indicating that it is destined to soon become occluded.\textsuperscript{8,71–73} Although a given severe (≥70\%) lesion is more likely to progress or totally occlude than a given mild or moderate lesion, clinical events are more frequently precipitated by lesions initially of the less severe type because these are much more numerous in the patient’s anatomy\textsuperscript{74} and also because the majority of occlusions of severe stenoses occur without an event.\textsuperscript{75}

A second insight was originally brought into focus by Constantinides\textsuperscript{76} but is receiving renewed attention.\textsuperscript{10,57,58,77–80} This is that, for the great majority of ischemic coronary events, a culprit lesion can be identified with variations of the following morphological features at histological examination: 1) a fissure, tear, or vent in the fibrous cap overlying the core lipid pool; 2) mural thrombus adherent at the site of the fissure; 3) bleeding into the core lipid region; and 4) severe arterial obstruction secondary to the composite mass of expanded plaque and thrombus.

Angiographic examples of plaques that have become unstable and caused a clinical event are shown in Figure 5. One can imagine the pathogenesis of each of these arteriographic examples in terms of the histological section in Figure 1B. Figure 5A shows a hemorrhagic pocket in the atheroma connected to the lumen by a narrow-necked fissure, or vent. In such cases, it has long been debated whether increased internal pressure in the plaque (caused by bleeding or by an inflammatory abscess) has burst the fibrous cap into the lumen or whether a primary fissure in the plaque permits bleeding into the core region. Figures 5B and 6 are almost certainly examples of hemorrhage into the plaque via an upstream fissure from the lumen, with resultant expan-
tion of the plaque and obstruction of flow when the fibrous cap is driven into the lumen. Figure 5C shows an angiographic finding commonly called "ulceration" of the plaque. It may have been formed by hemodynamic or proteolytic erosion of a thin fibrous cap to unroof the core lipid region or by an eruptive venting of a hemorrhagic plaque.

A third insight is that there are aspects of plaque lipid composition that predict the risk of fissuring. Fissures are literally absent from the arterial intima if there are no atheromata. Among patients who die of noncardiac causes, new fissures can be found in 9–17%, suggesting that not all fissures precipitate clinical events. The greater the core lipid content, the greater the likelihood of fissuring. Detailed histological assessment of 86 infarct lesions confirmed these findings; in 83%, the intimal fissure extended from the lumen into an unstructured pool of extracellular lipid. Yet, in any given patient, only a small subgroup of plaques (perhaps one in eight) has a substantial core lipid accumulation. A fourth insight is that certain aspects of fibrous cap composition predict the risk of fissuring. The macrophage density in caps that fissure is greater than that in intact caps. Fissuring occurs most commonly at the shoulder of an eccentric lipid-rich plaque (Figure 1B), a location of high macrophage density and also of high circumferential shear stress when there is significant core lipid, according to computer models of repeated pulsatile distention of the diseased arterial cross section. Finally, the fibrous cap is thinned and weakened by the lack of smooth muscle cells and lysis of collagen. Cytotoxic agents, including macrophage secretory products and oxidatively modified LDL, can transform a viable and structurally intact cap (Figure 1A) into one that is much more susceptible to fissuring (Figure 1B).

Prevention of Plaque Disruption

As described above, plaque fissuring is predicted by certain lipid-related aspects of plaque morphology including macrophage foam cell density, core lipid pool size, and possible cytotoxicity from oxidized LDL. Reduction of plasma LDL might be expected to reduce the likelihood of fissuring because of the experimentally demonstrated favorable effects of LDL reduction on these predictors. As a consequence, the frequency of abrupt progression to clinical events should decline among patients in whom LDL has been therapeutically reduced. Indeed, this has been the case. Analysis of 13 coronary events among 146 FATS patients reveals that the events were associated with a culprit coronary lesion in the distribution of worsening ischemia that progressed significantly in severity from the baseline stenosis measurement to that at the time of the event. As seen in Figure 7, the culprit lesions causing the great majority of cardiac events (eight of nine) among the conventionally treated patients arose from a pool of 414 lesions that were mild or moderate at baseline. By
Clinical events most commonly spring from lesions that are initially of mild or moderate severity and then abruptly undergo a disruptive transformation to a severe culprit lesion. The process of plaque fissuring, leading to plaque disruption and thrombosis, triggers most clinical coronary events. Fissuring is predicted by a large accumulation of core lipid in the plaque and by a high density of lipid-laden macrophages in its thinned fibrous cap. Lesions with these characteristics constitute only 10–20% of the overall lesion population but account for 80–90% of the acute clinical events. In the experimental setting, normalization of an atherogenic lipid profile substantially decreases the number of lipid-laden intimal macrophages (foam cells) and depletes cholesterol from the core lipid pool. In the clinical setting, intensive lipid lowering virtually halts the progression of mild and moderate lesions to clinical events. Thus, the reduction in clinical events observed in these trials appears to be best explained by the relation of the lipid and foam cell content of the plaque to its likelihood of fissuring and by the effects of lipid-lowering therapy on these "high-risk" features of plaque morphology. The composite of data presented here supports the hypothesis that lipid-lowering therapy selectively depletes (regresses) that relatively small but dangerous subgroup of fatty lesions containing a large lipid core and dense clusters of intimal macrophages. By doing so, these lesions are effectively stabilized and clinical event rate is accordingly decreased.

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