

Mechanisms of Acute Coronary Events

Based on a presentation by Daniel J. Rader, MD

Presentation Summary

A paradigm shift has occurred in the mechanisms of acute coronary events. Coronary atherosclerosis is now known to be a complex process involving a variety of interacting factors. Evidence supporting the new paradigm is provided through a brief review of the clinical trials that dispelled the old paradigm. Acute coronary events result from rupture of unstable plaques and are influenced by many mechanisms. Clinical trials have shown that management of high cholesterol with certain statins reduces the number of

acute coronary events. Reducing the number of acute coronary events is likely to involve a variety of mechanisms, many of which are unknown or poorly understood. There is a large group of people without symptoms who are at high risk for coronary heart disease. Many people in this group have normal cholesterol levels. Possible risk assessment techniques to identify them—laboratory testing and noninvasive imaging—are discussed. The mechanisms for reducing and preventing acute coronary events are the subject of much current research.

The mechanisms of acute coronary events are much more complex than was once believed, according to Daniel J. Rader, MD, Assistant Professor of Medicine at the University of Pennsylvania Medical Center and Director of the Preventive Cardiology and Lipid Research Center at the University of Pennsylvania Health System. It is now believed that atherosclerosis starts to develop when regional abnormalities and turbulent or nonlaminar flow cause activation of the endothelium at very specific areas in the coronary tree and other sites of the arterial tree. The activated endothelium at those sites expresses adhesion molecules, selectins, and other molecules. The abnormalities that result

cause transfer of leukocytes from the blood and make it more permeable to other atherogenic factors, such as low-density lipoprotein (LDL) and other types of lipoproteins. The LDL and other lipoproteins enter the vessel wall, become oxidized, and set up a local inflammatory response.

“One important concept that is really developing a lot more steam is that atherosclerosis is really a local inflammatory response within the vessel wall, and it is that inflammation that ultimately leads to the plaque that becomes unstable and ruptures,” said Dr. Rader. This local inflammation draws in more leukocytes, cytokines and growth factors which are secreted within the vessel

wall, and the LDL can be taken up by scavenger receptors and form the foam cells that lead to lipid-enriched plaques. Smooth muscle cells ultimately become involved. In the past, smooth muscle cells were thought to contribute to the formation of plaque, but it is now believed that they may provide a stabilizing influence.

The old paradigm on the mechanisms of acute cardiac events—disease progression over years and decades until coronary plaques became flow-limiting and stenotic, often caused symptoms such as exertional angina and positive stress tests, became plugged, and caused acute coronary events—has not been supported by the clinical trials of the past few decades. The angiographic statin trials—for example, Regression of Coronary Artery Disease as a Result of Intensive Lipid-Lowering Therapy in Men with High Levels of Apolipoprotein B (FATS), Monitored Atherosclerosis Regression Study, Canadian Coronary Atherosclerosis Intervention Trial, Multi-center Anti-Atheroma Study, Regression Growth Evaluation Statin Study, Pravastatin Limitation of Atherosclerosis in the Coronary Arteries, and Lipoprotein Cholesterol Atherosclerosis Study (LCAS)—all showed a statistically significant difference in angiographical findings between the treated group and the control group.

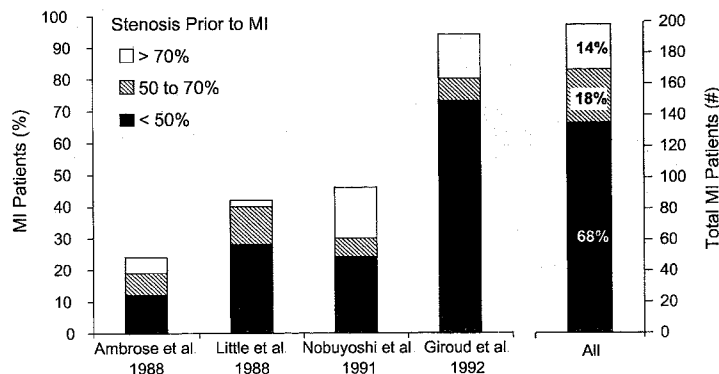
Within the last several years, these investigators have been reporting reductions in clinical events, some of which were remarkable, according to Dr. Rader. No direct relation was found between angiographic differences and reduction in clinical events. “It really suggests that there is something going on with these therapies that cannot be explained simply anatomically by changes in luminal diameter and suggests that clinical events may be the real gold standard that we want to focus on in making clinical decisions,” said Dr. Rader.

The FATS trial, one of the earliest angiographic prevention studies, provided one of the first observations that

not all acute coronary events are caused by lesions that are severely stenotic before the event. The concept was introduced that non-flow-limiting, less severely stenotic lesions had the potential to cause acute coronary events. A review of angiograms conducted at the start of the study showed that most acute coronary events were caused by lesions that were only between 30% and 60% stenotic.¹

A review of four trials by Falk et al published in *Circulation* provided additional evidence that many acute coronary events were caused by lesions that historically were considered unremarkable.² The trials—Ambrose et al, 1988; Little et al, 1988; Nobuyoshi et al, 1991; and Giroud et al, 1992—involved patients who underwent angiography because of symptoms or positive stress tests and within a few months had myocardial infarctions (MIs). The review indicated that 68% of all MIs were the result of lesions that were less than 50% stenotic, 18% resulted from lesions 50% to 70% stenotic, and only 14% resulted from lesions more than 70% stenotic (Figure 1).² “We have really started to re-examine our concepts of what types of lesions actually are likely to cause acute coronary events,” said Dr. Rader.

Figure 1. Most MIs Occur at the Site of a Previously Non-Flow-Limiting Coronary Lesion



Falk et al. *Circulation* 1995;92:657-671

The New Paradigm

Under the new paradigm, it is known that most acute coronary events are the result of a complex process involving many factors. Approximately 70% of all acute coronary events result from rupture of unstable plaques with less than

50% stenosis.² Rupture at vulnerable regions causes occlusive thrombosis. Unstable plaques are not flow-limiting, and therefore patients have no symptoms and normal stress tests.

People can develop a great deal of coronary atherosclerotic plaque and have essentially a totally preserved lumen at catheterization, because coronary vessels dilate at the site of a plaque and preserve the lumen for a long period of time. "We must start appreciating that a normal catheterization or even just little lumps and bumps do not necessarily mean that the patient does not already have significant coronary atherosclerosis," said Dr. Rader.

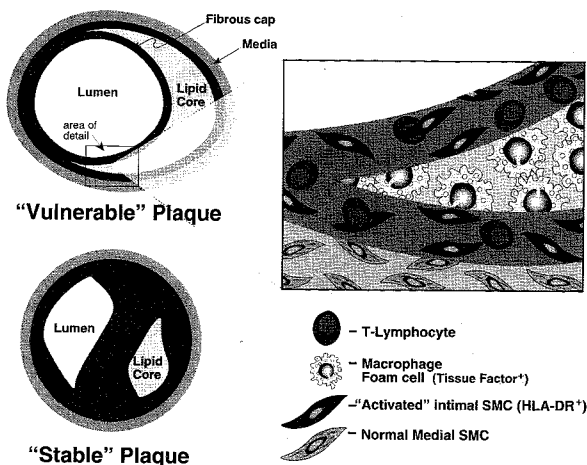
Most acute events are caused by lesions that are 30% to 60% stenotic and are not flow-limiting. These types of patients have no symptoms and would not be expected to have a positive stress test, and these lesions do not stimulate formation of collateral vessels. This type of lesion can be unstable. "There is something about lesions of this size that seems to make them more vulnerable to some sort of triggered acute event. We do not really know what exactly triggers that."

Something happens that results in fissuring or erosion of the overlying endothelium, exposing this thrombogenic plaque to blood space. A nidus of a thrombus can begin, which under the right conditions rapidly propagates to the point at which it occludes the rest or most of the rest of the lumen and causes an acute coronary event. The lack of collaterals in this type of lesion can result in a very large MI.

The new pathophysiologic paradigm for most acute coronary events necessitates new thinking on prevention of acute coronary events. Rather than focusing on stress testing and trying to determine who has stenotic lesions, the real task is trying to determine who has or is likely to have unstable plaques and implement strategies that have been proved to prevent disease progression.

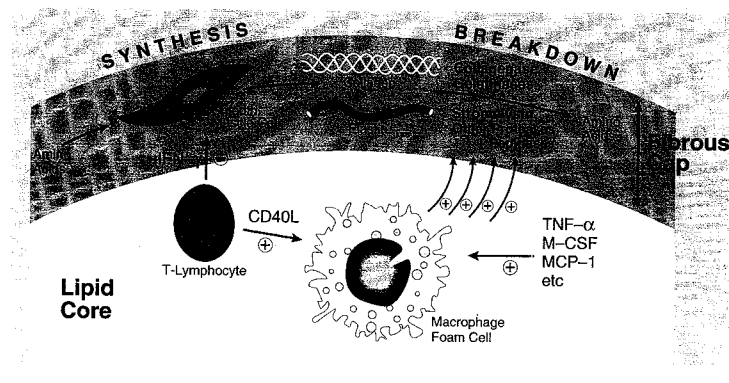
Why some plaques are unstable and likely to lead to an acute coronary event

Figure 2. Vulnerable and Stable Plaques



Libby P. Molecular basis of the acute coronary syndromes. *Circulation* 1995;11: 2846-2850. Reprinted with permission.

Figure 3. Factors Influencing the Fibrous Cap



Libby P. Molecular basis of the acute coronary syndromes. *Circulation* 1995;11: 2846-2850. Reprinted with permission.

is unknown. The characteristics of unstable plaques—a large lipid core, a thin fibrous cap, increased inflammatory cells, and reduced smooth muscle cell and matrix content—somehow make it more vulnerable (Figure 2).³ Stable plaques are characterized by a small lipid core, a thick fibrous cap, fewer inflammatory cells, and increased smooth muscle cell and matrix content (Figure 3).³ “We think our interventions that are reducing risk of acute coronary events are somehow taking at least a proportion of these unstable plaques and converting them to more stable plaques,” said Dr. Rader. The mechanisms are unknown. Current research is attempting to better characterize and understand unstable plaques and then determine how they can be converted to stable plaques.

Role of Reduction of Low-Density Lipoprotein Cholesterol

The effect on CHD of reducing cholesterol in the blood is not well understood. Reductions in LDL cholesterol (LDL-C) have been proved to reduce the number of clinical events in the angiographic statin trials, but the correlation between percentage LDL-C reduction and reduction in clinical events was not one-to-one.² Dr. Rader pointed out that although these trials were not designed or powered to analyze clinical event reduction, they still introduced the concept that although LDL-C reduction is an important component of the protective ability of these drugs to reduce risk for acute coronary events, there may be more involved in the complex stabilization of plaques.

Epidemiologic data from the Framingham study on the distribution of cholesterol levels among people with and those without coronary disease show tremendous overlap between the two groups.⁴ Thirty-five percent of all people who have or will have coronary heart disease have normal total cholesterol levels (less than 200 mg/dL).⁴ “If we only focus on people with obviously elevated cholesterol levels, we actually

miss the majority of people who are destined to develop coronary disease,” said Dr. Rader.

Factors Associated with Coronary Heart Disease and Mechanisms for Event Reduction

Although cholesterol is clearly an important component of coronary disease, many other factors and issues are involved in preventing coronary disease and acute coronary events. These are just beginning to be studied and include the prothrombotic state and endothelial dysfunction. Issues related to the thrombosis include aggregatability of

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platelets; fibrinogen levels, which are a determinant of thrombosis and plasma viscosity, another risk factor; and lysis of fibrin, which is one of the main components of plaque. Endothelial dysfunction is an issue not only in the development of atherosclerotic plaque but also potentially in the development of acute coronary events. This results in increased adhesion molecules and decreased nitric oxide production.

Potential mechanisms for reducing coronary events are plaque stabilization, enhanced formation of fibrous caps, reduced thrombus formation, anti-inflammatory effects, and restored endothelial function. In addition to their well-known ability to reduce LDL-C, statins have been shown to have other effects on cells in culture. In high concentrations, some statins affect proliferation of vascular smooth muscle cells and certain

types of tumor cells in vitro. Statins also may affect endothelial function, thrombus formation, and fibrinolytic activity, although more research is required.

Secondary and Primary Prevention: An Artificial Division

"Our whole division of prevention of coronary disease into secondary and primary prevention is a bit artificial," said Dr. Rader. "It is a useful way to talk about the data, but I think we all recognize that this differentiation is a bit artificial." Secondary prevention, treating people who have symptoms of coronary disease or other atherosclerotic vascular diseases, is literally just a small part of dealing with CHD in the United States. "These are the people who are lucky enough to have presented with symptoms without having died of their coronary event first," said Dr. Rader.

Primary prevention is much more controversial than secondary prevention and potentially much more expensive. Ultimately, however, it is likely to provide the most benefit for the resources invested. A tremendous number of people have subclinical atherosclerotic disease. Many of them have potentially vulnerable coronary lesions that are not flow-limiting and therefore not symptomatic. These people are at high risk for symptomatic coronary disease. There are also people who have multiple risk factors who are at risk for atherosclerosis. "This is really a continuum, and our goals are to get better at identifying which people are likely to go on to develop symptomatic disease and then really focus our resources on those people who are most at risk," said Dr. Rader.

Identifying people at high risk—people in a primary prevention setting—is the subject of active clinical research. Risk is considered in quantitative rather than definitive terms. Traditional risk factors are a starting point; unfortunately, many people with premature CHD do not have any obvious risk factors. A variety of clinical data can be put into risk models to determine the risk for an individual.

Laboratory testing and noninvasive vascular imaging may provide some answers to identification of higher-risk subgroups for more aggressive treatment. Dr. Rader cited the National Cholesterol Education Program guidelines, which include testing for high-density lipoprotein cholesterol (HDL-C) as a precedent for laboratory testing. The use of other tests appropriate to decision making on whom to treat—apolipoprotein B, small, dense LDL-C, lipoprotein A, and homocysteine—is currently being debated.

Noninvasive vascular imaging has the potential for use in the detection of established plaque. Carotid ultrasound scanning is currently the most common imaging technique used in this way. Coronary magnetic resonance imaging, cardiac positron emission tomography, and electron-beam computed tomography are other possible imaging techniques. The benefit of these techniques in this application has yet to be determined.

Conclusions

Acute coronary events are the result of a complex process. Most are caused by lesions that are not severely stenotic, often in people who have no history of CHD. Why some plaques are unstable and likely to cause events is unknown. Reductions in clinical events reported in the angiographic statin trials were shown to have no direct relation to angiographic differences, suggesting that clinical events should be the standard in making clinical decisions. Many factors in addition to lowering cholesterol are involved in preventing coronary disease and acute coronary events. Methods must be developed to determine who is at high risk for CHD.

FACULTY QUESTION-AND-ANSWER SESSION

Comment: By implication, you are making the radical statement that

catheterization and stress tests are out the door. I disagree.

Answer (Dr. Rader): We have to talk about quantitative risk, not just high or low. The average risk for an average 50-year-old male having an MI in the next 12 months is 1%. A normal stress test in him doesn't tell you more than you already know. I'm saying that stress tests are not the way to identify asymptomatic people who are at risk. It's a huge issue. We don't have ways of identifying prospectively and noninvasively people with vulnerable plaques. We have to use probabilities, like the Framingham model. Noninvasive tests are available, but they cost money. We're struggling with who should have these tests.

Question: *Could you comment on the effects of exercise on flow and atherosclerosis, both prior to the development of plaque and after plaque formation?*

Answer (Dr. Rader): The data strongly suggest that regular aerobic exercise has a long-term cardioprotective effect in terms of reducing coronary disease and acute coronary events. We don't understand why. Conversely, if someone who has an unstable plaque who hasn't been engaging in regular aerobic exercise suddenly exerts him/herself, the abrupt blood pressure or other changes that occur with significant exercise could be one factor that triggers the rupture of the unstable plaque and causes an acute event.

Question: *Your graph showed almost no risk of coronary artery disease with a cholesterol under 150. Are we not targeting a strict enough goal?*

Answer (Dr. Rader): That's not true. There is still risk even at very low cholesterol levels. Furthermore, that graph

is based on epidemiology. Epidemiology provides interesting ideas and hypotheses that then need to be tested in randomized clinical trials. We shouldn't base public policy about how we treat patients on epidemiology alone. Clinical trials show that the issue is more complicated than epidemiology makes it appear.

Question: *Most of us have to look at a cost-benefit analysis. What's the cost-benefit of a statin versus aspirin versus whatever when it comes to coronary disease?*

Answer (Dr. Rader): I don't believe we ought to be looking at it as something versus something else. We have every reason to believe that these interventions are additive or possibly even synergistic.

Comment: *Treating patients with established disease is the easy part, because the survivors of MI have shown that they are at high risk and they are easily identified. The challenge will be to identify the patients who are at high risk for MIs and determine how aggressively and when to treat them.*

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