

Impact of Risk Factor Modification on the CHD Process

Based on a presentation by Valentin Fuster, MD, PhD

Presentation Summary

Advances in technology have allowed better characterization of the atherosclerotic process and the plaques most likely to rupture and lead to thrombus formation. It has been established that the plaques most likely to rupture are those that are fat-filled with a thin fibrous cap. Modification of risk factors by lowering cholesterol appears to stabilize atherosclerotic plaques by decreasing the content of fat, causing the cholesterol to crystallize and the

fibrous cap to thicken. Macrophages are involved in plaque rupture and thrombus formation, and cholesterol lowering with a statin appears to prevent macrophages from entering the vessel wall and taking part in rupture and thrombus formation. High technology enables understanding plaque rupture and thrombus formation, but physicians need to apply this knowledge by implementing risk factor modification in the clinical setting.

Risk factors for coronary heart disease (CHD) were defined by the Framingham study¹ (Table 1). The more risk factors a person has, the higher the likelihood of CHD. Valentin Fuster, MD, PhD, Director of the Cardiovascular Institute at the Mt. Sinai Medical Center in New York explained the role of risk factors in the development of CHD. In the CHD process, he said, most risk factors influence the de-

velopment of the lesion most likely to rupture and lead to thrombus formation and coronary syndromes.

Lesions Prone to Rupture

The lesions that tend to cause coronary events do not necessarily make the artery narrow; on angiography, the artery appears normal in many patients. Nearly 70% of patients who present with an acute coronary syndrome have an artery leading to the syndrome that was less than 50% stenotic on a prior angiogram.

"The degree and the extent of primary artery disease on an arteriogram is no more than a marker to indicate that there are many small lesions that may rupture and lead to acute thrombotic events. It is not necessarily the severely stenotic lesions that cause coronary events," emphasized Dr. Fuster.

Since the angiogram does not necessarily identify vulnerable plaques, the

Table 1. Risk Factors for CHD

High Blood Pressure
Low HDL Cholesterol
Elevated Total Cholesterol
Cigarette Smoking
Diabetes

focus of study should shift to the plaque cells and the physical and chemical forces that affect plaque rupture, he continued.

“Specifically, it is important to understand that the plaque with a high content of fat and a very thin capsule is the most likely to rupture and lead to myocardial infarction (MI),” he told listeners.

These plaques have a high cholesterol content that makes them soft and they are contained by a thin fibrous capsule. Monocytes and macrophages can further weaken the plaque by digesting the extracellular matrix, making it more likely to rupture.

Prevention of Forces Leading to Plaque Rupture

Aggressive lipid-lowering therapy appears to modify the physical and chemical characteristics of the plaque lesion. A combination of recent studies showed that aggressive lipid lowering therapy resulted in a slight 1.4% regression of atherosclerotic lesions, but there was a 51% decrease in coronary events associated with this slight regression.²

“This appears to be a paradox. We have the miracle of decreasing coronary events without much change on the arteriogram. This leads to the question of what really happens to the plaque in order for the events to decrease,” continued Dr. Fuster.

Evidence From Recent Trials

The decrease in coronary events with aggressive lipid-lowering therapy seen in angiographic studies is paralleled by the decrease in mortality seen in recent secondary and primary prevention studies.

The Scandinavian Simvastatin Survival Study (4S)³ enrolled patients with CHD and hyperlipidemia (total cholesterol levels between 200 mg/dL and 300 mg/dL) and treated them aggressively with simvastatin. 4S was the first study to show a decrease in overall mortality for lipid-lowering therapy, as well as a decrease in coronary mortality and coronary events.

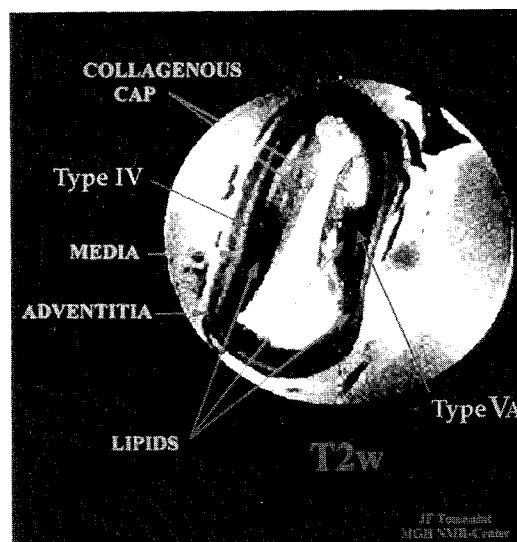
The Cholesterol and Recurrent Events (CARE)⁴ study enrolled CHD patients with total cholesterol levels between 200 mg/dL and 240 mg/dL. Again, a benefit in decreased numbers of coronary events was seen with aggressive lipid-lowering statin drug therapy.

The West of Scotland Coronary Prevention Study (WOSCOPS)⁵ was a primary prevention trial that enrolled patients with very high total cholesterol levels (>250 mg/dL). Aggressive statin therapy was associated with a significant decrease in coronary events.

Noninvasive Imaging for Study of Atherosclerotic Plaque

Over the past 2 years, new noninvasive technology has allowed more in-depth assessment of the atherosclerotic plaque. Using magnetic resonance imaging (MRI), changes in the plaque can be detected in vitro. In 1994, Dr. Fuster and colleagues obtained MRI autopsy images of plaques that are vulnerable to rupture. These are called the “Vb plaques.” The images showed that the plaques were fat-filled, with a very thin capsule and fragile appearance (Figure 1).

Figure 1. MRI Image of Two Lipid-Rich Plaques in the Aorta



"Animal studies and our recent MRI studies suggest that the reason coronary events significantly decrease when the anatomy doesn't change is because the composition of the plaque changes. The plaque becomes stabilized. There is less fat and more connective tissue that maintains the volume of the plaque," Dr. Fuster explained. "The fat that remains becomes crystallized and the plaque becomes hard and fibrotic, making it less likely to rupture and cause events," he added.

"Currently, we as physicians are not doing a good job in providing risk factor modification; only 30% of high-risk patients are being treated with lipid-lowering therapy."

—Valentin Fuster, MD, PhD

Dr. Fuster has recently been working with a colleague, M. Shinnar, MD, at Mt. Sinai Medical Center using MRI to study 80 carotid plaque specimens obtained with endarterectomy. Thus far, in the first 22 specimens, the sensitivity of MRI (as compared with histopathology) has been 90% in most of the plaque components.

"This is exciting, because in the near future we'll be able to use this technique in the carotid arteries in vivo for regression studies. This will help us understand what we are doing when we modify risk factors," Dr. Fuster said.

The two researchers have also used MRI in porcine studies in vivo and preliminary results suggest that this technique is feasible for assessing left anterior descending coronary lumen and plaque composition, following percutaneous transluminal coronary angioplasty (PTCA) of a normal artery. A collaborative effort is being established with Dr. Sidney Smith's group at Chapel Hill to study animals with induced fatty lesions in the left anterior descending coronary artery.

"We are excited about this research. We are getting very close to being able to study the coronary artery in vivo, and it will not be long before we can use this technology in humans," he commented.

The Thrombogenic Component

The thrombogenic component of plaque is modified by risk factor modification, Dr. Fuster said. He and colleagues found that plaques in the coronary arteries that had the highest content of lipid also had the highest content of tissue factor, or thromboplastin, a chemical that initiates the cascade of the coagulation system. This occurs in the area where the macrophages are found.

"The same macrophages involved in rupture are thrombogenic and lead to the blood clot. These macrophages are involved in acute events and are traitors to health," said Dr. Fuster.

These macrophages have been identified in the in vivo rabbit using positron emission tomography studies. In rabbits fed a high-cholesterol diet, monocytes are visualized in the vessel wall of the aorta. These monocytes can be modified by lipid modifying agents, he explained.

"When a statin is used, it prevents macrophages from entering the vessel wall," he added.

Conclusion

High technology enables visualization of the atherosclerotic process and understanding what happens when risk factors are modified. This knowledge is not enough to make sure that high-risk patients are treated appropriately.

"Currently, we as physicians are not doing a good job in providing risk factor modification; only 30% of high-risk patients are being treated with lipid-lowering therapy," Dr. Fuster stated.⁶

"In summary, we are beginning to understand what happens by preventing risk factors. But we have a problem. We are not preventing them," Dr. Fuster concluded.

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