

## Surrogate Endpoints and Newer Risk Markers in Atherosclerosis Management

*Based on a presentation by Christie M. Ballantyne, MD*

### **Presentation Summary**

Trials with clinical events as the primary endpoint inherently have poor sensitivity to detect therapeutic effects on plaque stabilization and thrombosis because most plaques that rupture do not cause symptoms. Blood tests or imaging modalities that correlate to the burden or activity of atherosclerosis may provide surrogate endpoints to assess therapeutic efficacy in both clinical trials and clinical practice. For surrogate endpoints to be valid in clinical trials, they must be biologically plausible (ie, related to the disease process) and altered by therapies that decrease the endpoint for which they are used as a substitute. Examples of surrogate endpoints include progression of coronary disease assessed by angiography, intravascular ultrasound, and other imaging techniques. Risk assessment may be refined and therapy better monitored with blood tests that measure novel markers of atherosclerotic disease. Markers that have been shown to be associated with atherosclerosis include C-reactive protein, intercellular adhesion molecule 1, interleukin-6, and fibrinogen.

**A**lthough most clinical events are caused by plaque rupture or erosion, which may result in thrombosis, most plaques that rupture do not cause symptoms. Therefore, trials that measure only clinical events do not detect the majority of plaque ruptures because these ruptures are asymptomatic. Trials based solely on clinical event reduction inherently have poor sensitivity to detect therapeutic effects on plaque stabilization and thrombosis,

therefore they provide limited information for individualizing therapy. Because of this limited assistance from clinical trials, much attention has been given recently to the development of surrogate endpoints in atherosclerosis management.

The concept of the surrogate endpoint is well illustrated in a 52-year-old patient who underwent percutaneous transluminal angioplasty with stent placement 6 months ago and a transurethral retropubic prostatectomy for prostate cancer 1 month later. The patient takes a statin and aspirin for heart disease and hormone replacement for prostate cancer. Follow-up visits with the urologist and cardiologist are scheduled for the same day.

In addition to discussing symptoms related to urinary flow, the urologist measured the patient's prostate-specific antigen (PSA) level to assess tumor burden and thus gauge therapeutic efficacy. If the PSA was elevated, noninvasive imaging techniques, such as ultrasound, magnetic resonance imaging, and computed tomography, could be used to refine assessment of disease burden and recurrence. If indicated, a biopsy can be performed; however, use of the known surrogate markers (blood and imaging tests) may prevent this invasive procedure from being required. The urologist's determination of therapeutic efficacy is not limited to the patient's symptoms (specifically, urine flow).

The cardiologist asked the patient whether he had been having any chest

pain and performed a treadmill test to assess blood flow to the myocardium. However, this information could not provide an answer to the patient's straightforward question, "How are my plaques doing?" Although the cardiologic assessment relies on many noninvasive techniques to ascertain adequate blood flow (eg, observed and reported symptoms, stress test results), invasive procedures such as coronary catheterization are required to measure plaque burden. However, these procedures still do not provide information on plaque stability.

Surrogate endpoints for atherosclerosis management must be biologically plausible; that is, they must be related to the processes of atherosclerosis, plaque instability, and thrombosis. Surrogate endpoints must also be altered by therapies that decrease the endpoint for which they are being used as a substitute. Surrogate endpoints currently examined in clinical trials include coronary artery disease progression as assessed by quantitative coronary angiography and intravascular ultrasound, magnetic resonance imaging, B-mode and 2-D ultrasound, and quantitative assessment of coronary calcium by ultrafast computed tomography.

#### **Molecular Basis of Atherosclerosis**

The molecular basis of atherosclerosis also provides the framework for the biologic plausibility of surrogate endpoints. Advances in molecular and cellular biology and genetics have greatly increased our understanding of the molecular mechanisms of atherosclerosis: The atherosclerotic disease process has been shown to include a complex series of events involving alterations in vascular endothelial function, smooth muscle cells, extracellular matrix, and lipoproteins. Fundamental in the pathophysiology of this disease process is inflammation. Leukocytes appear to be involved in atherogenesis, plaque rupture, thrombosis, and ischemia/reperfusion injury. The adhesion of circulating monocytes and lymphocytes to the vascular endothelium with subsequent

transendothelial migration is a critical event in atherogenesis. Cell adhesion molecules, which mediate the adhesion of leukocytes to endothelial cells, have consistently been discovered in areas of atherosclerotic plaque development. In clinical studies, levels of soluble cell adhesion molecules have been shown to be associated with dyslipidemia.

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#### **New Risk Markers**

The Atherosclerosis Risk in Communities (ARIC) study, which included approximately 16,000 men and women between the ages of 45 and 64 years, evaluated the incidence of coronary heart disease events (fatal or nonfatal myocardial infarction and surgical revascularization procedures), and carotid artery atherosclerosis (assessed by B-mode ultrasonography). The investigators found that a high level (fourth quartile) of intercellular adhesion molecule-1 (ICAM-1) increased the risk for a coronary event 5.5-fold, after adjusting for race, age, gender, body mass index, hypertension, diabetes, total cholesterol, high-density lipoprotein cholesterol (HDL-C), triglycerides, cigarette smoking, von Willebrand's factor, fibrinogen, and white blood cell count. They also found that individuals with either ICAM-1 or E-selectin in the fourth quartile had a higher risk for carotid artery atherosclerosis.<sup>1</sup>

The Physicians' Health Study also found that high levels of ICAM-1 were associated with increased risk for myocardial infarction that increased progressively over time, suggesting that a

low-grade chronic inflammation may contribute to the development of atherothrombotic disease.<sup>2</sup>

Smaller studies have shown that lipid-modifying therapy can alter levels of soluble cell adhesion molecules. In one study of aggressive lipid modification in patients with severely elevated low-density lipoprotein cholesterol (LDL-C) levels (in the range seen with familial hypercholesterolemia), atorvastatin or simvastatin combined with colestipol lowered the levels of soluble E-selectin. In another study, in individuals with high triglyceride levels, treatment with fish oils reduced triglyceride levels by almost 50% and reduced the levels of soluble E-selectin and ICAM-1 as well, with the greatest reductions observed in patients with diabetes, who also had the highest triglyceride levels at baseline.<sup>3</sup>

Other inflammatory markers associated with atherosclerosis include C-reactive protein (CRP), interleukin-6, serum amyloid A, and fibrinogen. At this time, the high-sensitivity assay for CRP (hs-CRP) has the greatest evidence for clinical utility because of the consistent epidemiologic data, a standardized assay that is commercially available, clinical trial data that show that patients with elevated hs-CRP benefit from therapy with aspirin or statins, and finally, data that statins lower both hs-CRP and reduce clinical events.<sup>4,5</sup> However, data from the West of Scotland Coronary Prevention Study (WOSCOPS) show that hs-CRP weakens with regard to relative risk after adjustment for age, systolic blood pressure, triglycerides, and LDL-C and HDL-C levels.<sup>6</sup> The WOSCOPS investigators found that lipoprotein-associated phospholipase A<sub>2</sub>, which may be a mediator of vascular inflammation, was strongly associated with risk for a coronary heart disease event, and that association was not confounded by other risk factors.

#### Future Directions

With the completion of the Human Genome Project and rapid advances in gene array technology, it may soon be

possible to study alterations of gene expression in atherosclerotic lesions. New genetic polymorphisms that are associated with coronary heart disease may also be useful to identify new molecular markers. Another major advance will likely be in the area of proteomics, which will permit identification of proteins that are differentially expressed in atherosclerotic lesions or in endothelial cells exposed to “atherogenic” stimuli.

#### Summary

Surrogate endpoints may refine the identification of patients at high risk for atherosclerotic and thrombotic events and may improve the assessment of therapeutic efficacy. To be useful clinically, these clinical endpoints (eg, myocardial infarction, cardiovascular death) must be biologically plausible—that is, related to the process of atherosclerosis and plaque instability—and they must be altered by therapies that decrease the endpoints for which they are surrogates.

#### QUESTION-AND-ANSWER SESSION

*Question from the Audience:* Do you consider ankle-brachial index (ABI) measurements useful in assessing risk in patients with diabetes?

*Dr. Ballantyne:* I think ABI measurement, which is probably underutilized, is useful if we talk about a simple noninvasive test that does have important predictive value. Another test that may be underutilized, if you look at data from WOSCOPS, is an electrocardiogram showing nonspecific ST-segment changes. It is another way of identifying high-risk individuals.

The question that arises is whether all people with diabetes have a coronary heart disease equivalent. I think the answer is probably “no.” We will probably treat it that way in the next set of guidelines, but there are some adults with diabetes who are at higher risk than others. The general risks are so high that I am

not sure we have to do an ABI on everybody, but people with diabetes would be a group to test to screen for peripheral vascular disease.

**Question from the Audience:** *What about the aggressive treatment? Dr. Waters commented on this approach in the discussion following his presentation. Do you agree with his theory? Do you agree that more is better?*

**Dr. Ballantyne:** I am a therapeutic enthusiast. I advocate aggressive therapies to lower LDL-C further and raise HDL-C. However, in 1992, when many clinicians argued about whether to treat cholesterol, we had already established a lipid clinic, as well as a section for atherosclerosis treatment instituted in 1975. We felt that the scientific basis and the clinical trial data provide adequate support, although the evidence was not conclusively definitive until the Scandinavian Simvastatin Survival Study. Current data are similar for more aggressive LDL-C reductions combined with efforts to raise HDL-C. We have enough data on both lipid profiles to be make clinical judgments and formulate national policy guidelines.

I certainly try to lower LDL-C very aggressively in my patients and I try to raise HDL-C to more than 40 mg/dL in patients who have atherosclerosis.

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