Technology Assessment

Technology Assessment Program

Agency for Healthcare
Research and Quality
540 Gaither Road
Rockville, Maryland 20850

Vulnerable Plaques: A Brief Review of the Concept and Proposed Approaches to Diagnosis and Treatment

January 22, 2004

Vulnerable Plaques: A Brief Review of the Concept and Proposed Approaches to Diagnosis and Treatment

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January 22, 2004

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Appendixes

GLOSSARY

ACE – angiotensin converting enzyme

ACS – acute coronary syndrome

AMI – acute myocardial infarction

CAD – coronary artery disease

CMS – Centers for Medicare & Medicaid Services

CT – computed tomography

CVD – cardiovascular disease

IVUS – intravenous ultrasound

MI – myocardial infarction

MRI – magnetic resonance imaging

OCT – optical coherence tomography

PTCA – percutaneous transluminal coronary angioplasty

US – ultrasound

VP – vulnerable plaque

1. INTRODUCTION

The Centers for Medicare & Medicaid Services (CMS) requested from the Agency for Healthcare Research and Quality a brief review of the diagnosis and treatment of vulnerable plaque (VP) of coronary and carotid arteries. The Tufts-New England Medical Center Evidence-based Practice Center was asked to conduct this review. The aims of this report were to:

1. Review the concept(s) of VP.
2. Review any literature and/or statements from experts about the natural history of VP.
3. Review the various methods that have been suggested or actually used to diagnose this condition.
4. Review any information that may be available regarding the conceptual framework, which would inform the evaluation of such diagnostic techniques (e.g., what reference standard would be used in determining the accuracy of a proposed test?).
5. Review any literature and/or statements from experts about how VP, once identified, would be treated.
6. Review how the existence of methods for identifying VP may change the types of treatments or the types of patients who get treatment for carotid or coronary artery occlusions.

2. METHODS

This brief review is intended to be used as a "horizon scan" to inform CMS about the current concept of so-called VP and how it might affect the usage of existing or developing diagnostic and therapeutic technologies. As such, this report is not a detailed technology assessment based on a systematic review of the literature. It does not synthesize or evaluate the results of individual clinical studies and it does not make clinical recommendations.

It should be noted that because the concept of VP is still evolving, it is not an established medical diagnosis. Therefore, any reference to VP in this report concerning its natural history, diagnostic methods, and treatments is by necessity inferential. It refers to conditions that might fall under the current concept of VP and it is not specifically about VP per se. We have taken this broad approach in our review in order to include potentially relevant articles that would otherwise be overlooked in answering these questions. In this report, we will use the term "VP" in quotes to denote that the entity being discussed is yet to be defined and that it refers to conditions related to the current concept of VP. This approach is taken to avoid the awkwardness of repeating these caveats every time the VP concept is mentioned.

Thus, the objective of this review is to retrieve and examine recent publications that describe the current concept of VP and to collect basic information about diagnostic tests and treatments that have been proposed or used to evaluate patients with "VP."

Literature Search Strategy

A literature search was conducted on October 8, 2003 to address the aims of this report. The MEDLINE and MEDLINE In-Process & Other Non-Indexed Citations databases (formally PreMEDLINE) were searched to identify English language publications. Because VP is an

emerging concept, there are no specific medical subject headings (MeSH terms). Text words were therefore used exclusively. The MEDLINE search strategies used are listed below:

1.   (instab$ adj6 plaque$).tw.   246
2.   (unstab$ adj6 plaque$).tw.   388
3.   (atheroma adj6 plaque$).tw.   195
4.   (ulcer$ adj6 plaque$).tw.   700
5.   (vulnerab$ adj6 plaque$).tw.   381
6.   or/1-5   1731
7.   exp Dental Deposits/   13620
8.   exp Multiple Sclerosis/   22264
9.   exp Skin Diseases/   354890
10.   6 not (7 or 8 or 9)   1555
11.   limit 10 to human   1458
12.   limit 11 to English language   1173

The results of the MEDLINE search from 1966 through the search date produced 1,173 abstracts. Search results of the MEDLINE In-Process & Other Non-Indexed Citations database yielded 61 additional abstracts. We selected abstracts published since 1998 to understand the current thinking about the VP concept. We also selectively retrieved articles of special interest or relevance published before 1998.

Selecting and Reporting Relevant Studies

We retrieved and reviewed about 150 articles. We selected review articles, commentaries, and editorials to review the concept of VP. We used clinical studies that reported original data as well as review articles to gather information about diagnostic tests, treatments, and the natural history of "VP." Because none of the clinical studies that reported original data explicitly defined the term "vulnerable plaque" and used it as the inclusion criterion, we used our judgment to select studies in clinical settings that are within the broad range of the current concept of VP.

The results of the literature review are organized into the following sections in this report according to the aims. Section 3 summarizes the current concept. Section 4 reviews data on the natural history. Section 5 summarizes diagnostic tests that have been proposed or used. Section 6 reviews proposed treatments. Section 7 discusses how the existence of methods for identifying VP might change the types of treatments or the types of patients who receive treatment for carotid or coronary artery occlusions.

3. CURRENT CONCEPT OF VULNERABLE PLAQUE

Acute coronary syndrome (ACS–acute myocardial infarction (AMI) or unstable angina) occurs when the myocardial demand for oxygen exceeds the supply from the coronary arteries. Typically, this condition is due to atherosclerotic coronary artery disease (CAD). As atheromatous plaque builds up on the wall of the coronary arteries, it compromises the lumen of the artery. This condition may be diagnosed with coronary angiography, which provides a radiographic image and measurement of the luminal diameter. Classically, stenotic plaques which compromise the coronary arteries by more than 60-70 percent are viewed as potentially

clinically or hemodynamically significant and place a patient at higher risk for ACS. This provides the rationale for coronary revascularization procedures.

However, many serial angiographic studies have demonstrated that most acute myocardial infarctions (AMI) occur due to occlusion of coronary arteries that did not previously contain significant stenosis, and that the coronary artery with the most severe stenosis is usually not the "culprit" artery (i.e., the one causing AMI) (Little 1988; Ambrose 1988). Thus, plaque progression and clinical outcome are not always closely related, and each is poorly predicted on clinical and angiographic grounds. In the past decade, it has become clear that most plaques that underlie a fatal or nonfatal MI are less than 70 percent stenosed angiographically (Kullo 1998; Kolodgie 2001).

These observations have led to the development of the concept of VP. Researchers have suggested that the immediate precursor of most of the culprit plaques for ACS is plaque that is at high risk of rupturing and not just the plaque that is stenotic (Davies 1997; Kullo 1998; Kolodgie 2001). The VP is the "short-term precursor" to the culprit plaque, which triggers clinical ACS (i.e., unstable angina and AMI). The concept of the VP has been developed largely by histopathological studies of culprit lesions in the coronary circulation of patients who have died from AMI and is evolving now using imaging techniques and other methods in living subjects.

Plaques of the coronary arteries are characterized by a lipid core encased in a fibrous "cap". Although these plaques may compromise the lumen of the coronary artery and thus be visible on angiography (which visualizes only the vessel lumen and not the vessel wall), it is estimated based on histopathological studies of "culprit" plaques that approximately 60 to 70 percent of AMIs are caused by plaque rupture, with release of the thrombogenic core of lipid and necrotic debris (Davies 1990; Falk 1995). Less frequently—30 to 40 percent on histopathology—thrombi are seen to overlie denuded endothelium, suggesting an erosion of the cap (Davies 1990; Falk 1995). According to this concept, VPs are those plaques at high risk for rupture, or at high risk for having the surface of their fibrous cap denuded, in either case leading to thrombus formation. Thus, determining the degree of stenosis by angiogram, currently the routine method relied on for clinical decisionmaking, will be quite unreliable in predicting future disease since gradual occlusion of the lumen by a progressing stenotic plaque is not felt to be a major cause of AMI.

Instead, based on histological studies of culprit plaques, VPs are generally felt to have three histologic hallmarks compared to stable plaques (Davies 1997; Kullo 1998; Kolodgie 2001; Forrester 2002): a larger lipid core (>40 percent of total lesion area), a thinner fibrous cap (65 to 150 micrometers), and many inflammatory cells.

In addition to the above triad, others (Goldstein 2002; Monroe 2002) have noted certain angiographic features that distinguish patients with ACS from those with stable CAD—complex coronary stenoses and/or coronary plaque fissures/erosions.

Based on the above described "structural" concept of the VP, multiple diagnostic methods have been proposed to identify VPs, including angiography, intravenous ultrasound (IVUS), angioscopy, thermography catheters, optical coherence tomography (OCT), magnetic resonance imaging (MRI), and computed tomography (CT). These methods are currently in the investigational phase, since none is supported by large, prospective natural history studies or by clinical studies demonstrating risk reduction.

In addition to the local features described, there is some evidence that systemic factors may play a role in plaque instability (Rothwell 2000; Naghavi 2003a), including the presence of

a systemic inflammatory state. This provides the rationale for the search for serum biomarkers to identify patients with high-risk lesions.

Recently, a review article from a large group of investigators has described a broader concept of VP (Naghavi 2003a). According to this broader concept, the VP signifies any plaque that might cause clinically significant CAD. Thus, the plaque that is vulnerable to rupture and/or denudation is but one sub-type of VP. Nevertheless, it is clearly the major sub-type, and along with "vulnerable myocardium" and "vulnerable blood," "vulnerable plaque" forms the triad of vulnerability that defines the "vulnerable patient." Other lesions prone to causing symptomatic coronary artery disease are depicted in the figure below taken from this review.

Different Types of Vulnerable Plaque
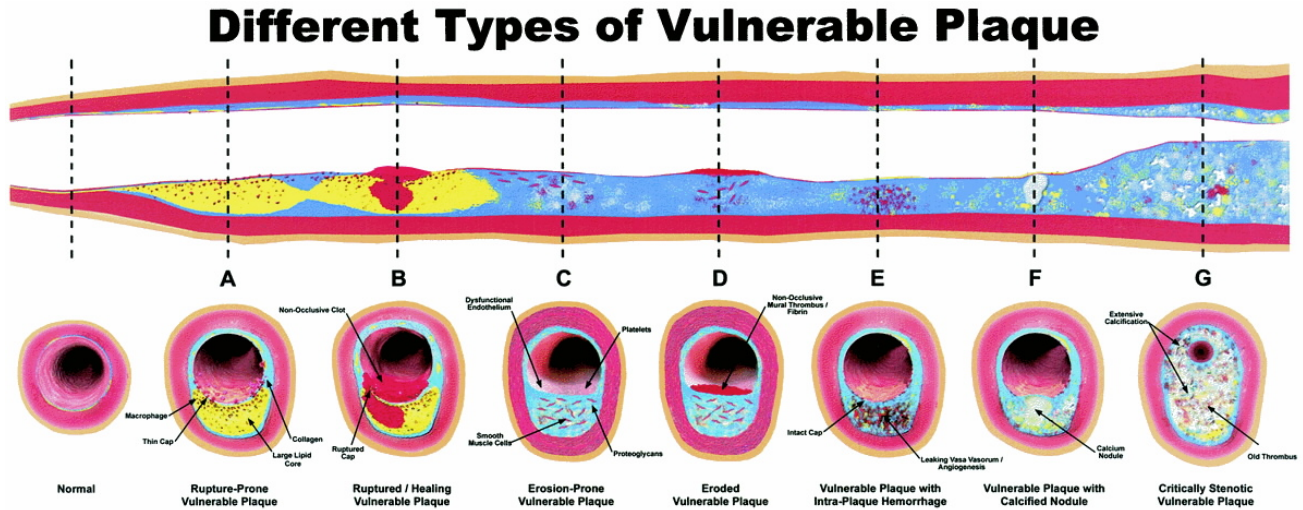
Different types of vulnerable plaque as underlying cause of acute coronary events (ACS) and sudden cardiac death (SCD). A, Rupture-prone plaque with large lipid core and thin fibrous cap infiltrated by macrophages. B, Ruptured plaque with subocclusive thrombus and early organization. C, Erosion-prone plaque with proteoglycan matrix in a smooth muscle cell-rich plaque. D, Eroded plaque with subocclusive thrombus. E, Intraplaque hemorrhage secondary to leaking vasa vasorum. F, Calcific nodule protruding into the vessel lumen. G, Chronically stenotic plaque with severe calcification, old thrombus, and eccentric lumen (from Naghavi M, et al. Circulation 2003;108:1664-1672 (Figure 2). Permission to use figure and legend granted by Lippincott, Williams & Wilkins; http://lww.com).

The "classic" description of the VP is represented by "Plaque A." Despite the fact these authors also consider the other plaques vulnerable, there is consensus that Plaque A (i.e., that histological type most prone to rupture) is the most characteristic lesion. These authors agree that roughly 70% of culprit lesions are caused by rupture and the remaining 30 percent of culprit lesions (i.e., non-ruptured) are caused by erosion (Plaque C), the presence of a calcified nodule (Plaque F), or another cause. Therefore, they have proposed criteria for defining VP based on this broader definition. Major criteria include: active inflammation (monocyte/macrophage +/- T-cell infiltration), thin cap with large lipid core, endothelial denudation with superficial platelet aggregation, fissured plaque, and stenosis > 90 percent. Minor criteria include: superficial calcified nodule, glistening yellow appearance, intraplaque hemorrhage, endothelial dysfunction, and outward (positive) remodeling.

As we cautioned earlier in the methods section, although we repeatedly use the term "vulnerable plaque" in the remainder of this report, this usage should not be construed as an affirmation of the validity of the concept described above. Additional studies are needed to either validate or refute this concept.

Stroke is another major cause of cardiovascular disease (CVD) in which the concept of VP might be applicable to carotid artery lesions. However, it should be noted that the concept concerning VP is derived mostly from the CAD literature; the data on carotid artery disease is even more limited.

4. NATURAL HISTORY OF VULNERABLE PLAQUE

Assuming the validity of the VP concept, in order to investigate its natural history and estimate the risk of clinically significant plaque rupture or ACS over time based on aspects of plaque morphology, plaque thermography, or biochemical markers, an investigator would need a prospective longitudinal cohort study that would in many aspects resemble the Framingham Study. We describe below the design of a hypothetical study to understand the natural history of "VP."

A study would need to enroll a population sufficiently large and sufficiently high-risk (e.g., age 55 with either diabetes mellitus, known CAD, or at high cardiovascular risk according to their Framingham score (>10 percent risk over 10 years)) and followed for a sufficiently long enough time to provide a sufficient number of outcomes to determine which features are important in determining the risk of plaque rupturing. In addition to collecting routine data such as age, gender, presence of diabetes mellitus, hypertension, and known CAD, the cohort should be serially assessed with the following modalities:

- Using one or more of the most promising techniques (e.g., IVUS, OCT, thermography) to characterize the lesions. Because characterizing the lesion in this detail would require invasive techniques and is not intended to alter patient-management or to benefit the patient (who is either asymptomatic or may have only stable angina), this approach may be difficult to justify ethically. It may, therefore, be necessary to begin with a safer albeit inferior technology (e.g., CT angiography).
- Serially measure serum biomarkers, including cellular and inflammatory markers such as hs-CRP, IL–6, IL–18, and MMP–9. Even though these markers have not been explicitly studied for plaques that fall within the proposed VP concept, they have been demonstrated to be associated with ACS events in previous studies.

At the time of any clinical outcomes (ACS events) the culprit lesion should be determined. Using this database, clinical, laboratory, and imaging data can be used to predict the likelihood that a specific plaque will lead to clinically significant events, and what characteristics of plaque morphology and/or biochemistry best predict the likelihood of plaque rupture or progression.

Review of Natural History Studies that Focus on Atherosclerotic Lesions that Progress

Since there is no standard definition for VP, there are no natural history studies for this proposed concept. However, several studies have characterized plaques with angiography at baseline. Additional follow-up data were available to provide some insights into what VP studies, once a standard definition is achieved, might reveal. The studies described below

investigated the association of lesion morphology with atherosclerotic progression or ACS occurrence.

Chester (1996) assessed the behavior of complex coronary plaques and diameter stenosis changes in 222 patients with chronic stable angina without prior ACS events. These patients were waiting for single vessel PTCA and underwent serial angiograms. They found that complex stenoses (i.e., poorly defined, irregular, or scalloped borders, abrupt edges to lesions, ulceration, presence of filling defect consistent with thrombus) progressed by 3±13 percent compared with 0.5±7 percent among the smooth (absence of complex features) stenoses (p=0.15). Complex stenoses were 4.2 times more likely to progress than smooth stenoses. The data from that study demonstrated that morphologically complex stenosis may develop without an episode of symptomatic ACS and that individual complex lesions are at a higher risk of progression than individual smooth lesions.

Goldstein (2000) analyzed angiograms from 253 patients for complex coronary plaques characterized by thrombus, ulceration, plaque irregularity, and impaired flow. The data showed that patients with multiple complex plaques, in contrast to those with single complex plaques, were at risk of increased incidence of recurrent ACS (19 percent vs 2.6 percent, p<0.001).

Haft et al. (1993) compared the natural history of smooth coronary lesions with complex lesions. They reported that of 255 patients who had 2 to 4 serial arteriograms within 2.6±1.7 years, 203 patients had a significant coronary lesion on at least one arteriogram. Of 167 patients without intervening coronary bypass surgery, there were 48 complex irregular lesions and 141 smooth lesions on followup arteriograms. Irregular lesions progressed more often than did smooth lesions. The authors concluded that the plaque lesions could be grouped into two major categories of progression: (1) gradual growth of a smooth-walled plaque rupture; or (2) plaque rupture with marked progression to severe irregular lesion.

As part of the Coronary Artery Surgery Study (CASS), which randomized 780 patients to an initial strategy of medical therapy versus bypass surgery, Alderman et al. (1999) evaluated follow-up angiograms at 5 years to identify clinical and angiographic features associated with progression of CAD. Of the 3,888 segments assessed, 2,938 non-bypassed coronary segments in 298 patients were evaluated. Percent stenosis was directly proportional to the risk of a lesion progressing to complete occlusion, in contrast to the findings cited above (Little 1998; Ambrose 1988). Complex stenosis morphology defined as multiple closely spaced lesions and diffuse disease was noted to correlate with disease progression. However, the CASS system of grading of morphology, performed in the 1970s, did not include the more detailed features incorporated in more recent conceptualization of VP.

In a study of 31 men who died suddenly of ischemic heart disease, Mann et al. (1999) examined 39 coronary arteries containing 256 plaques. The authors reported that 16 of 99 plaques (16 percent) with less than 20 percent diameter stenosis showed prior healed disruption on histology. For those arteries with 21 percent to 50 percent stenosis, 16 of 86 plaques (19 percent) showed healed disruption. Fifty-two of 71 plaques (73 percent) with ≥ 51 percent stenosis had healed disruption. This finding that most of the high-grade stenotic lesions had prior episodes of plaque disruption suggests that disruption is a stimulus to plaque growth and is a major factor in causing chronic high-grade coronary stenosis.

5. PROPOSED METHODS TO DIAGNOSE VULNERABLE PLAQUE

Imaging modalities that have been used to study plaques within the current concept of VP are summarized in this section. Under the current concept of VP, most CVD events are caused by plaques at high risk of rupture. Therefore, studies of biomarkers predicting CVD events might be useful to identify the presence of "VP." We reviewed studies that examined the association between serum biomarkers and the occurrence of ACS events. Since these are not studies of specifically defined "VP" populations, their inclusion here is merely to suggest possible roles of these biomarkers.

The evaluation of a diagnostic test requires a reference standard. Given the lack of a reference standard for VP, we discuss some issues concerning such a definition. This discussion is followed by summaries of peripheral blood biomarkers and imaging modalities. We provide one table for blood biomarkers (Table 1) and another for imaging tests (Table 2). Appendices 1 and 2 provide detailed descriptions of each biomarker and imaging test, respectively.

Reference Standard Issues of Tests for Vulnerable Plaque

The current concept of VP focuses on the characterization of the structure and behavior of the plaque lesion. Given the location of the plaques and the need to accurately characterize intra-luminal plaque features, an invasive imaging technology will most likely be used as the reference standard for VP. It will be necessary to conduct natural history studies (as discussed earlier in Section 4) to compare these tests to determine the technology that most accurately predicts the occurrence of ACS or acute ischemic neurological events.

Assuming the validity of the concept of VP, a peripheral blood marker could potentially be used for diagnostic purposes if it was unique to the VP features and if it was sufficiently elevated to be detected by a laboratory method before the plaque ruptures. Considering that most cellular markers are far from being specific because they usually come from more than one part of the human body, it would be difficult to distinguish whether the increased level of a marker was due to these plaques or to some other process such as inflammation unrelated to the coronary arteries.

Additionally, complex techniques might be required for the detection of certain markers. Furthermore, a plaque with vulnerable features must be identified reasonably quickly to allow for effective therapies to be instituted. Traditional risk assessment predicts long-term outcome, but does not provide information about whether a specific plaque will rupture in 1 month, 6 months, or 1 year. This raises the question of how the diagnostic threshold value of a marker would be established.

Ideally, to evaluate a peripheral blood marker to diagnose the condition, we would need a prospective study of subjects that would be followed for outcomes attributable to plaque rupture (ACS or sudden death). In this ideal study, baseline measurements of the marker with the properties already described, as well as the results of the imaging technique, should be obtained.

The imaging technique would allow us to focus on certain segments of coronary arteries that may correspond to VPs and which would serve as a reference standard to test the proposed marker. After an outcome, new imaging studies (or autopsy) would confirm whether the event was due to the rupture of one of those segments that was initially characterized as VP. At the end of follow up, the data would be analyzed to determine whether there was a relationship between the baseline values of the cellular marker and the outcomes that were attributed to VPs.

Such a prospective cohort study would face several barriers. These include the need to use invasive techniques in an apparent healthy population, the difficulty of obtaining complete followup data on the study population, the lack of a reference standard for imaging techniques as well, and the difficulty of selecting one of the proposed markers to be tested since none meets all the requirements.

Studies of Inflammatory and Cellular Markers

Candidate markers have been evaluated by prospective studies for predicting clinical outcomes—ACS or cerebrovascular events, or death. Since they may identify singly or in combination only those patients at risk for those outcomes, their association with plaque vulnerability must be inferred.

The paradigm for peripheral blood biomarker detection for "VP" is predicated on the principle that cytokines and other biologic factors within the plaques can enter or leave the bloodstream, and be detected circulating in peripheral blood. Alternatively, "VP" may cause unique cell types, cytokines, or a combination of substances and cells to appear in the peripheral blood of affected patients (Schwartz 2003). Finally, certain types of patients, i.e., those with a systemic inflammatory state or those prone to producing inflammatory markers, might be more likely to form "VP."

Although unique identifying substances that would permit high sensitivity and specificity have not yet been characterized, several candidate markers have been proposed that may be used to estimate the "VP" risk in populations (Schwartz 2003). This non-invasive assessment of risk could be used to identify patients for future non-invasive or invasive imaging studies.

Table 1 summarizes inflammatory and other cellular markers that have been evaluated by prospective studies for predicting cardiovascular or cerebrovascular events. A narrative descriptive of these markers is included in Appendix 1.

Table 1. Inflammatory and other cellular markers that have been evaluated in clinical studies to assess association with CVD clinical outcomes

Marker	Studies Have Been Conducted on Population Without Known CAD[*]	Laboratory Method	Clinical Outcome Predicted
C-Reactive Protein (hs-CRP)	Yes	Latex-particle enhanced immunoassay	MI, RV, stroke, death
Matrix Metalloproteinase9 (MMP–9)	No	ELISA	Death
Soluble Intercellular Adhesion Molecule-1 (sICAM-1)	Yes	ELISA	MI, stroke, death
Soluble Vascular Cellular Adhesion Mollecule-1 (sVCAM-1)	No	ELISA	MI, stroke, death
Soluble E-selectin (sE-selectin)	Yes	ELISA	MI, stroke, death
Interleukin-6 (IL–6)	Yes	ELISA	MI, death

Interleukin-18 (IL–18)	No	ELISA	MI, death
Tumor Necrosis Factor-alpha (TNF-alpha)	No	uantitative enzyme immunoassay	MI, death
Soluble CD40L (immunomodulator)	Yes	ELISA	MI, stroke, death

* All of these markers have been studied in populations with known CAD

CAD: coronary artery disease; MI: myocardial infarction; RV: revascularization; ELISA: enzyme linked immunosorbent assay

Review of studies that used a biomarker to assess ACS risk

Several studies described below investigated prospectively whether cellular and inflammatory markers are associated with progression of ACS.

Blankenberg et al. (2002) evaluated serum concentration of IL–18 and other markers of inflammation in 1,229 patients with CAD and found IL–18 to be a strong independent predictor of cardiovascular disease (CVD) death in patients with CAD; the authors suggested that IL–18-mediated inflammation leads to accelerated vulnerability of atherosclerotic plaques.

Blankenberg et al. (2001) evaluated the effect of soluble adhesion molecules on the risk of future cardiovascular events among 1,246 patients with CAD with a mean 2.7 years of follow-up. They concluded that soluble adhesion molecules level of sVCAM-1, sICAM-1 and sE-selectin were significantly related to future death from cardiovascular causes among patients with CAD.

Chakhtoura et al. (2000) evaluated 25 patients (17 with unstable angina and 8 with stable angina) and found that patients who had unstable complex lesions had a fivefold higher expression of the platelet activation epitope CD63 than patients with stable angina. In addition, patients with unstable angina had 15 percent more glycoprotein IIb/IIIa aggregation sites expressed on their platelet membrane. A direct relationship was observed between the morphology of ruptured plaque and platelet activation in patients with unstable angina.

Considering the studies available in the published literature, the hs-CRP measurement appears to be the strongest marker for future clinical events (i.e., MI, unstable angina, and stroke) due to arterial inflammation in both diseased and apparently healthy, asymptomatic patients (Morrow 2000; Koenig 1999; Tracy 1997; Reuben 2000; Biasucci, Liuzzo, and Fantuzzi 1999; Ridker 1998; Kuller 1996; Taaffe 2000; Danesh 2000; Lowe 2001). The CRP plasma level is also suggested as the best method of risk assessment in patients with either stable or unstable angina (Liuzzo 1994; Heeschen 2000; Biasucci, Liuzzo, and Grillo 1999; Sabatine 2002; Morrow 1998; Toss 1997) and for long term assessment after MI (Ridker, Rifai, Pfeffer, et al. 1998).

Furthermore, significant lipid elevation occurs in fewer than 50 percent of patients with ACS, MI, and unstable angina. For this reason, cholesterol and lipid measurement alone do not seem to be satisfactory markers for those at risk of sudden vascular events. One study (Ridker, Stampfer, and Rifai 2001) showed CRP and Total/HDL cholesterol ratio as the only cardiovascular risk indicators, using multivariate and age adjusted analysis. If CRP, IL–6 and ICAM–1 levels are added to lipid levels, risk assessment can be improved over lipids alone (Ridker, Stampfer, and Rifai 2001). Appendix 1 describes each marker and its potential association with clinical outcomes in detail.

In summary, although there is some indication that cellular markers might be correlated with ACS risk (i.e., they suggest the presence of VP), there is no evidence from studies specifically designed to evaluate whether such markers can accurately predict the presence of "VP."

Imaging Modalities

Development of clinically useful imaging techniques for identifying "VP" has been an active area of research in the last decade. Table 2 lists non-invasive and invasive imaging modalities which have been proposed and studied to assess these plaques. Appendix 2 describes each modality and its potential association with clinical outcomes in detail.

Table 2. Imaging modalities that have been used or proposed to evaluate "VP" and similar conditions (modified from MacNeill 2003; Fayad 2001)

Imaging Modality	Spatial Resolution (μ)	Vessel Wall Penetration (mm)	Image of vessel wall	Fibrous Cap	Lipid Core	Inflammation	Calcium	Thrombus	Comments
Invasive Methods									
Angiography		NA	*				*	*	Reference standard for stenotic lesions
Intravascular Ultrasound (IVUS)	40 ~ 100	~10	*	*	*		*	*	Characterizes vessel wall and morphology, good for calcified plaque, poor for lipids
Angioscopy	Visual	Poor	*	*	*			*	Direct visualization of lumen surface, using color and surface appearance to identify vulnerable plaques
Optical Coherence Tomography (OCT)	2~30	1~2		*	*	*	*	*	Provides cross-sectional images of vessel wall and quantifies fibrous cap thickness and extent of lipid collections
Thermography	500	Poor				*			Images temperature heterogeneity due to rise in temperature in macrophage-rich areas in plaque
Raman Spectroscopy	NA	1~1.5		*	*	*	*		Analysis of Raman spectrum for chemical composition of atherosclerotic plaque
Near infrared Spectroscopy		2							
Intravascular MRI	160	Good		*	*	*	*	*	Measurements of cap thickness and characterization of atherosclerotic lesion
Non-invasive Methods									
Surface Ultrasound	400	Good	*	*	*		*	*	Characterizes vessel wall and morphology, good for calcified plaque, poor for lipids
Computed Tomography		NA					*	*	More useful for detection of calcified plaques
Nuclear Scintigraphy	Poor	NA			*			*	Based on specific binding of radioactive labeled molecules to the target tissue (such as radiolabeled LDL)
Standard MRI	300	Good		*	*	*	*	*	Measurements of cap thickness and characterization of atherosclerotic lesion

Summary of Methods to Diagnose Vulnerable Plaque

Despite the rapidly growing support for the VP concept among the research community, current clinical practice has not been substantially altered by this concept. This is largely because there is not yet a consensus on the operational definition of a VP, and there is no readily available imaging or laboratory test that would allow clinicians to diagnose the presence of a VP in routine clinical practice. Moreover, even if such a diagnostic test were available, too little is known about the natural history of "VP," so it is difficult to see how such a diagnostic test would inform clinical decisionmaking at this time. Further, there are substantial barriers to the development of accurate diagnostic methods of the plaques. One major barrier derives from the

fact that the description of the plaques was based largely on histopathological descriptions of culprit lesions. This gold standard is only available after a plaque becomes a culprit plaque, and indeed only after the patient dies. Large-scale studies of the natural history of plaques are needed, to identify what characteristics on the various imaging modalities are most important in prospectively predicting plaque rupture. These studies have not been done to date.

Among the imaging techniques described above, a clear consensus has not emerged about which method should be the reference standard, nor has a unique identifying substance such as CRP been identified that would uniquely identify these plaques with any reasonable sensitivity or specificity. Therefore, it is our opinion that large scale, prospective studies employing serial imaging of the coronary arteries of asymptomatic high-risk patients, or of patients with stable angina, is required before an estimate of the risk of an acute coronary event can be made either in asymptomatic patients or in patients with stable angina with plaques of a particular morphology.

In summary, the clinical diagnosis of VP remains problematic. Currently, neither invasive nor non-invasive imaging technology can reliably identify VP prospectively, i.e., before rupture.

6. PROPOSED TREATMENT OF VULNERABLE PLAQUE

Conceptual Basis for Treatment

Based on the current concept of the VP, clinical strategies for preventing ACS can now be framed as promoting plaque stability. In a literature review, Forrester (2002) identified 5 stages of plaque destabilization, including: (1) endothelial activation; (2) LDL entry into vessel wall; (3) LDL activation; (4) breakdown of the fibrous cap; (5) thrombus formation. In the same review, he proposed six mechanisms by which anti-atherosclerotic therapies may exert their therapeutic effects: (1) improve endothelial function; (2) decrease LDL levels; (3) inhibit LDL oxidation; (4) increase reverse cholinesterase transport; (5) reduce inflammation; and (6) inhibit thrombosis.

Proposed Treatments for Vulnerable Plaque

Endothelial dysfunction is believed to promote inflammation, and inflammatory cell activity can contribute to "VP"; therefore lipid-lowering drugs, including statins, are recommended to reduce inflammation and improvement of endothelial function. Matrix metalloproteinase (MMP) activity may also contribute to the plaque rupture. Statin therapy may reduce this risk by decreasing collagen degradation (Corti, Farkouh, and Badimon 2002; Corti and Badimon 2002).

ACE inhibitors such as ramipril may have direct or indirect effects on plaque stability (Corti 2002). Ambrose (2002) suggests using ACE inhibitors and beta-blockers to stabilize plaques by reducing the circumferential stress on the fibrous caps. ACE inhibitors improve endothelial function, reduce inflammation of the vascular wall, and may induce the synthesis and release of interleukin-6 from macrophages. Antithrombotic agents such as aspirin were recommended to reduce platelet aggregability. Other agents that may promote plaque stability include antioxidants and macrolide antibiotics. Anti-inflammatory agents, including inhibitors of MMP, were also suggested.

Rabbani (1999) reviewed single agent and combination therapies, including statins alone or in conjunction with anti-lipemic agents, niacin and/or diet, diet alone or with exercise and stress management, partial ileal bypass, beta-blockers, ACE inhibitors, and anti-oxidants. Other theoretical therapies include: gene therapy, MMP inhibition, reduction in inflammatory cell infiltration, and macrolide antibiotics.

Zaman et al. (1999), suggested drug interventions such as: lipid-lowering and antioxidants agents (to help stabilize the plaques by reducing the lipid content, harden the fibrous tissue, and reduce MMP activity in the plaque), ACE inhibitors (to improve endothelial dysfunction), antibiotics (for the anti-chlamydial or anti-inflammation properties), beta-blockers (to reduce cap fatigue by the reduction of stresses in the arterial walls).

Treatment modalities such as phototherapy, cryotherapy, or thermotherapy have been discussed as potential therapies along with drug-eluting stents by Baim (The Gray Sheet, Sept 29, 2003). A multifaceted approach described by Corti (2002) includes lifestyle modifications and medications, such as statins and ACE inhibitors. Kereiakes (2003) advocated a systemic approach that includes statins, clopidogrel, ACE inhibitors, fibrates, thiazolidinediones, low molecular weight heparins, platelet glycoprotein IIb/IIIa receptor antagonists, and cyclooxygenase 2 inhibitors.

On the basis of two studies of plaque morphology in carotid arteries, endarterectomy (AbuRahma 1998; Lal 2002) was suggested to manage stenosis once the "VP" had been identified. A review article indicated that, in selected cases, "high-risk zones of vulnerable plaque" may be treated by "invasive/catheter-based strategies, including photodynamic or sonodynamic activation of photosensitizer/sonosensitizer agents…" These agents "… localize within plaque inflammatory/smooth muscles cells or by targeted site-specific drug delivery." This author also speculated about the future potential of "novel drug-eluting stent platforms" for treating certain types of stenoses (Kereiakes 2003).

Mechanical interventions, including stenting, were not mentioned as potential therapeutic approaches to VP in the review articles we examined for this report, including those articles that focused primarily on therapeutic strategies (Rabbani 1999; Zaman 1999; Libby 2001; Forrester 2002). The use of invasive treatment modality for "VP" appears to be at most only a minor theme in the current literature.

Review of Articles Reporting Treatments Related to "VP"

Review of the literature identified four articles that assessed treatments related to potential therapeutic mechanisms of "VP." Three articles, including one case report, examined the effect of treatments on the progression of carotid artery plaques. One randomized controlled trial examined the effectiveness of antibiotics for the prevention of a secondary event for the patients who had MI. There were no primary prevention studies for CAD.

Thies (2003) studied the effect of fish oil on 53 subjects in a 3-arm randomized controlled trial. All 162 patients were scheduled for carotid endarterectomy and the morphology of the excised plaques was evaluated. Fewer plaques from patients who took fish oil (long chain omega-3 fatty acids) had a thin fibrous cap and signs of inflammation compared with the controls.

Another study examined five hypercholesterolemic subjects with carotid artery plaques verified by ultrasound. After a 1-year intervention of cerivastatin, their plaque stability index (percentage of total plaque lesion on echogram as a high intensity region) improved significantly (Kurata 2001).

A case report of a hyperlipidemic, hyperhomocysteinemic, 78 year- old male showed a regression of the carotid plaque area following the use of folate, pyridoxine, and cyanocobalamin. Ultrasound was employed to evaluate the stability of the carotid plaque (Spence 2002).

The recently completed WIZARD trial (Weekly Intervention with Zithromax (azithromycin) for Atherosclerosis and its Related Disorders) tested the hypothesis that chronic infection may contribute to the pathogenesis of atherosclerosis. Thus, the elimination of chronic infection with an antibiotic will lead to reduced systemic inflammation and lower the risk of future ACS events. Survivors of AMI were treated with an antibiotic, azithromycin, for 11 weeks and followed for approximately 3 years. Among stable patients with previous MI and with evidence of C-pneumoniae exposure, azithromycin did not significantly reduce the clinical sequelae of CAD (O'Connor 2003).

7. IMPLICATIONS FOR PATIENT MANAGEMENT

Assuming that the VP concept is, on the whole, accurate, then the current medical therapy, as it is effective in preventing CAD, is presumably also effective in preventing these plaques from developing or in stabilizing existing plaques. As discussed above, current therapies frequently used in CAD in which the mechanism of action may include stabilization of the plaque include, most notably, statin therapy and ACE inhibition, as well as beta-blockade. Additionally, as described above, PTCA and carotid endarterectomy have been recommended. Although by no means a major theme in the scientific literature that we reviewed, there appears to be considerable interest in stenting as a potential treatment, as evidenced by a recent report on CBS News:

> Daniel Simon, M.D., director of interventional cardiology at Brigham & Women's Hospital in Boston, in a recent analyst call, referred to drug-eluting stents as the 'perfect pacifying device' for VP. He said that the use of drug-eluting stents in treating VP could triple annual stent procedures (Anonymous, CBS news, Sept 20, 2002).

Whether Dr. Simon's prophecy will prove to be true is a matter of speculation. However, we believe there are considerable barriers to evidence-based prophylactic stenting of VPs, some of which we highlight below.

1. These plaques are typically asymptomatic, since they are, by definition, precursor lesions; many of the methods proposed to diagnose these plaques (e.g., OCT, IVUS, and angioscopy) are invasive procedures, typically reserved for patients with clinical syndromes such as unstable angina and AMI. Apparently the great majority of such plaques occur in patients who do not present such clinical syndromes.
2. In this review, we did not identify any large scale, population-based natural history studies using a priori defined plaque characteristics. Thus, although it may be that plaques that were structurally vulnerable cause most clinical events, the probability that a plaque with "vulnerable" characteristics (using any of the emerging technologies) will cause a clinically significant event is still unknown. Furthermore, since it may be hard to justify research protocols requiring invasive testing on asymptomatic individuals, even those at relatively highrisk of atherosclerosis, natural history studies are problematic to contemplate. Regarding natural history, we speculate that if the condition is common,

then the risk that any identified plaque will rupture must be rather low. On the other hand, if the risk that a plaque will rupture is high, then VP resulting in clinical events should be relatively rare.

3. Prophylactic stenting of VP would have considerable competition from pharmacological treatments. First-line treatment for patients at risk for symptomatic CAD is aspirin, statins, and ACE inhibitors. Since stenting presumably would not replace pharmacotherapy, stenting would have to show significant benefit compared to medication. Furthermore, pharmacologic therapies themselves are evolving. For example, intravenous administration of recombinant HDL (ApoA-1 Milano) (Nissen 2003— a variant of apolipoprotein—caused regression of coronary atherosclerosis. This suggests that pharmacologic therapies may improve substantially, even further reducing the risk that an identified VP will lead to a clinical event. Indeed, the concept of the VP may produce other effective pharmacologic approaches, such as inhibitors of MMP activity, which might further diminish any putative benefits to prophylactic stenting.

8. SUMMARY

The concept of VP is still evolving. We can only speculate about its course since no studies have been designed to accurately describe the natural history based on plaque characteristics. In such a context it is not surprising that there is only limited inferential evidence regarding methods of diagnosis and treatment modalities of this condition.

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APPENDIXES

Appendix 1. Description of Selected Inflammatory and Other Cellular Biomarkers that Have Been Evaluated in Clinical Studies to Assess Association with CVD Clinical Outcomes

C-reactive protein (hs-CRP)

CRP is produced by the liver, appears in peripheral blood, and is a sensitive marker of inflammation. Atherosclerotic plaques contain CRP, generally associated with accumulation of complement (a molecule that is activated during inflammation and which activates other inflammation molecules) and macrophages or foam cells (Zaman 1999). Multiple studies now suggest CRP as an independent risk factor for atherosclerotic vascular disease (Haverkate 1997, Zebrack 2002, Morrow 2000, Koenig 1999, Tracy 1997, Westhuyzen 2000, Ridker 1997). Several studies show that high hs-CRP levels predict poor prognosis for patients with unstable angina (Liuzzo 1994, Tomoda 2000, Heeschen 2000). However, the specifics of diagnostic potential for VP are still being defined.

The matrix metalloproteinases (MMPs)
MMPs are proteolytic enzymes produced by macrophages that digest extracellular matrix, eroding the fibrous cap of the atheromatic plaque resulting in its thinning and further weakening (Zaman 1999). Several MMPs have been identified in atherosclerotic plaque, playing key roles in vascular remodeling (Schwartz 2003).
Plasma MMP–9 concentration was identified as a novel risk marker of future cardiovascular mortality in a large cohort of patients with CAD independently of main clinical and therapeutic confounders (Blankenberg, 2003).

Cellular Adhesion Molecules (CAMs)
Specific adhesion molecules on the endothelial surface act as receptors for monocytes and T cells. They mediate adhesion of circulating leukocytes and their subsequent transendothelial migration (Zaman 1999). Such adhesion molecules include several selectins, intercellular adhesion molecules (ICAM), and vascular cellular adhesion molecules (VCAM).
The Physicians' Health Study showed that baseline sICAM-1 and sE-selectin correlated with cardiovascular risk (Ridker, Rifai, and Stampfer 2000). Furthermore, CAMs exhibited independent coronary and cerebrovascular risk in the Atherosclerosis Risk in Communities (ARIC) study (Hwang 1997).
sICAM-1 is predictive also in apparently healthy people, whereas sVCAM-1 and sE-selectin have a strong predictive value mainly in those patients with atherosclerotic lesions or at least risk factor-induced inflammation resulting from activated endothelium (Blankenberg 2001).

Interleukin-6 (IL–6)

Cytokine IL–6 is prominent early in focal inflammation. Its implication with vascular inflammation is consistent since it is the principal initiator of hepatocyte CRP expression (Schwartz 2003).

IL–6 appears to predict short-term (Biasucci, Liuzzo, and Grillo 1999) and long-term (Lindmark 2001) mortality of CAD patients having experienced one or more episodes of instability. Furthermore, several studies (deLemos 2000; Haverkate 1997; Haverkate 2000; Ridker, Rifai, and Stampfer 2000) of healthy adults have shown an association between elevated IL–6 levels and cardiovascular mortality and future MI.

Interleukin-18 (IL–18)

IL–18 induces interferon (IFN)-γ production in T lymphocytes and natural killer cells, which is believed to play a crucial role in atherosclerotic plaque rupture (Zaman 1999). Baseline measurement of IL–18 provides powerful information for future fatal cardiovascular events across the entire spectrum of patients with stable or unstable CAD (Blankenberg 2002). IL–18 exhibited a weak correlation with hs-CRP, IL–6, and MMP–9. Combined determination of MMP–9 and IL–18 has been suggested to identify patients at very high risk (Gerdes 2002).

Tumor Necrosis Factor (TNF)-alpha

TNF-alpha is a proteolytic enzyme produced by macrophages that digest extracellular matrix, eroding the the fibrous cap of the atheromatic plaque resulting in its thinning and further weakening. Thus, it facilitates vessel wall damage and contributes to plaque vulnerability.

TNF-alpha (the level increases following MI) and is a marker for increased cardiac event risk. It is suggested that since TNF-alpha has a short serum half-life, it might have limited value for long-term prognosis (Ridker, Rifai, Pfeffer et al. 2000).

Soluble CD40 Ligand (sCD40L)

SCD40L is a multi-potent immunomodulator expressed with its receptor on the vascular endothelial cells, smooth muscle cells, mononuclear phagocytes, and platelets. Its ligation on the surface of these cells triggers the expression of various pro-inflammatory mediators (Schonbeck and Libby 2001). In a prospective, nested case control analysis among participants in the Women's Health Study, high plasma concentrations of sCD40L appeared to be associated with increased vascular risk in apparently healthy women (Schonbeck, Varo, and Libby 2001).

Appendix 2. Description of Imaging Modalities That Have Been Evaluated in Clinical Studies to Characterize the Plaque Morphology

Invasive Imaging

Angiography

Traditionally, angiography is the reference standard for identifying coronary and carotid artery lesions. It provides information about the luminal diameter and enables visualization of the luminal surface to diagnose atherosclerotic disease. Angiography may show severe lesions, plaque disruption, luminal thrombosis, and calcification. Other than some calcifications, angiography does not provide information about the vessel wall or atherosclerotic plaque composition such as the vulnerable lipid-rich plaques or other histopathological features (Topol 1995). A major limitation of angiography is that diffuse atherosclerotic disease may narrow the entire lumen of the artery, and therefore underestimate the degree of local stenosis. Additionally, some outwardly displaced plaques may appear to have normal luminal diameter despite significant disease (Glagov 1987).

Intravascular Ultrasound

Catheter-based intravascular ultrasound (IVUS) is an imaging modality to detect atherosclerotic plaque distribution to characterize vessel wall and plaque morphology (Regar 2002). Coronary atheroma can be classified into categories based on plaque echogenicity: (1) highly echoreflective regions with acoustic shadows, often corresponding to calcified tissue; (2) hyperechoic areas representing fibrosis or microcalcifications; or (3) hypoechoic regions corresponding to thrombotic or lipid-rich tissue or a mixture of these elements (Nissen 2001). The main limitations of IVUS include poor resolution and inability to discriminate between fibrous and lipid-rich plaques (MacNeill 2003). Modifications of this technique using analysis of integrated backscatter and the radiofrequency envelope might improve resolution (Kawasaki 2002). IVUS elastography that combines US images with radiofrequency measurements may be able to better detect regions of increased strain prone to rupture (de Korte 2000).

Angioscopy

Intracoronary angioscopy facilitates direct visualization of the plaque surface, color of the luminal surface, presence of thrombus, and macroscopic features of the arterial wall (Uchida 1995). The normal appearance of the vessel surface is glistening white. A white granular plaque may appear at the site of plaque rupture because of the platelet-rich thrombus. Yellow plaques correspond to the lipid-rich core and thin fibrous cap that characterize the site as vulnerable. A red, irregular surface protruding into the lumen may indicate fibrin or erythrocyte-rich thrombus (Mizuno 1991, Ueda 1996). Angioscopy visualizes the luminal surface but is insensitive to subtle differences in plaque. Therefore, the major role of angioscopy has been assessing lumen structure before and after interventions (Mizuno 1992).

Thermography

Thermography is a catheter-based technique to detect heat released by activated inflammatory cells of atherosclerotic plaques. Temperature differences correlate positively with cell (macrophage) density, which may predict plaque disruption and thrombosis (Cassells 1996, Stefanadis 1999). However, there is no clear evidence that temperature differentials correlate with specific plaque vulnerability. Finally, without the structural definition obtained from high-resolution imaging techniques, the independent role of thermography is limited (Stefanadis and Toutouzas 2002).

Optical Coherence Tomography

Optical Coherence Tomography (OCT) measures the echo time delay and intensity of backscattered light due to internal microstructure in the tissue (Fujimoto 1999). OCT can provide high resolution, cross-sectional images of arterial wall. Fibrous, lipid, and calcified components of VP have been discerned by OCT (Yabushita 2002). Limitations of OCT for in vivo intravascular imaging include limited tissue penetration depth, reduction of image quality when imaging through blood or large volumes of tissue, and a relatively slow data acquisition rate (Fujimoto 1999). OCT elastography is also being evaluated by combining high-resolution imaging with radiofrequency measurements to detect foci of increased strain that are prone to plaque rupture (MacNeill 2003).

Raman Spectroscopy

Raman spectroscopy is an intravascular optical technique that characterizes the tissue's chemical composition. The Raman spectrum is obtained by processing the collected light scattered by tissue when illuminated with a laser. The molecular characteristics of lipid and calcium salts make Raman spectroscopy highly sensitive for plaque detection (Brennan 1997). Although, Raman spectroscopy is one-dimensional, it could be combined with other catheter-based imaging techniques, such as IVUS, to localize and quantify cholesterol and calcium salts in atherosclerotic plaques (Romer 2000).

Near Infrared Spectroscopy

Near infrared spectroscopy (NIRS) measures diffuse reflectance signals by using near infrared light as an energy source. Similar to Raman spectroscopy, NIRS also yields information about tissue chemical composition (Zhu 2000). NIRS may detect the lipid core and features of plaque vulnerability of the fibrous cap and inflammation (Moreno 2002). A limitation of this non-contact spectroscopic modality is that it is influenced by flowing blood, and its lack of structural definition restricts its independent use in VP detection (Cassis 1993).

Intravascular Magnetic Resonance Imaging

To improve the resolution of magnetic resonance imaging (MRI), an intravascular coil is inserted in the artery or the adjacent vein (Hofmann 2001). Intravascular Magnetic Resonance Imaging (IMRI) yields adequate resolution to discriminate plaque components, including lipid, collagen, thrombus, and calcium on the basis of biochemical properties (Fayad 2000). Technical limitations exist in the IMRI coil designs, requiring multiple catheter manipulations and repeated imaging. Image quality is also reduced significantly as the intravascular coil moves off axis from the external magnet field (MacNeill 2003).

Noninvasive Imaging

Magnetic Resonance Imaging

MRI can be used as a non-invasive imaging method to assess lipid cores, fibrous caps, calcification, normal media, adventitia, as well as intraplaque hemorrhage and acute thrombosis. MRI yields images without using ionizing radiation and can be repeated sequentially over time (Toussaint 1996).

MR angiography (MRA) and high-resolution black-blood imaging of the vessel wall can be combined. MRA demonstrates the severity of stenotic lesions and their spatial distribution, while the high-resolution black-blood wall characterization technique may show plaque composition and may facilitate the risk stratification and selection of treatment (Yucel 1999). Recently MRI has been used to measure the effect of lipid-lowering therapy (statins) in asymptomatic, untreated hypercholesterolemic patients with carotid and aortic atherosclerosis (Corti 2001).

Ultrasound

Because echogeneity of the plaque reflects its characteristics, surface ultrasound (US) can non-invasively assess plaque in the carotid vessel. Measurements of carotid wall thickness as well as qualitative and quantitative analysis of plaque can be taken. Hypoechoic heterogeneous plaque is associated with both intraplaque hemorrhage and lipids, while hyperechoic homogeneous plaque is mostly fibrous (Cohen 1997, Nissen 2001).

Ultrafast Computed Tomography

Atherosclerotic calcification is found more frequently in advanced lesions, and may occur in small amounts in early lesions (Wexler 1996). Ultrafast Computed Tomography (UFCT) allows image acquisition of plaque calcification more reliably and rapidly than conventional computed tomography (CT). Fast imaging is essential to eliminate cardiac and respiratory motion artifacts. Only electron-beam CT (EBCT) and fast-gated helical or spiral CT can measure the amount or volume of calcium (Callister 1998). However, high-risk plaques often lack calcium. While, the relation of calcification to unstable plaque remains unclear, coronary calcification as detected by EBCT seems to be an indicator of atherosclerotic burden (Moreno 2000).

Nuclear Scintigraphy

Many proteins labeled with various radioisotopes have been evaluated on the basis of molecules and cells involved in atherogenesis (Vallabhajosula 1999). These include lipoproteins (native LDL and oxidized LDL), immunoglobulins against macrophages, smooth muscle cells, endothelium adhesion molecules, and antifibrin antibody fragments and peptides (which bind to glycoprotein IIb/IIIa receptors on activated platelets) (Vallabhajosula 1997, Vallabhajosula 1988, Iuliano 2000). No single radiotracer is ideally suited to image atherosclerosis and providing the prognostic and clinical indicators necessary for medical and surgical interventions (Vallabhajosula 1999).