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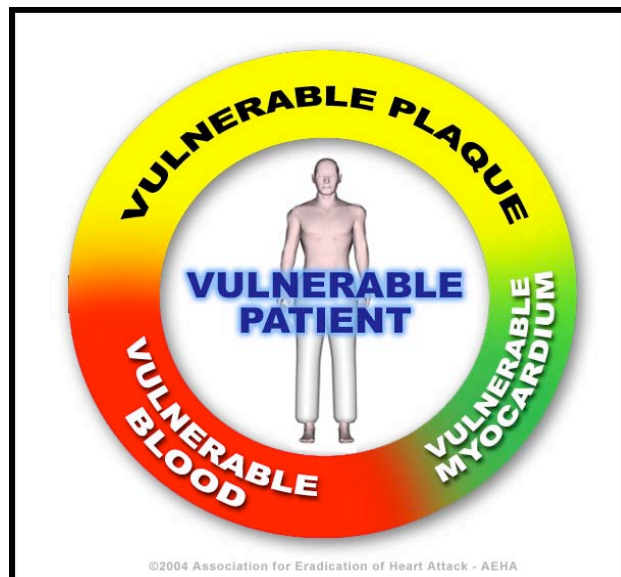
VULNERABLE PLAQUE

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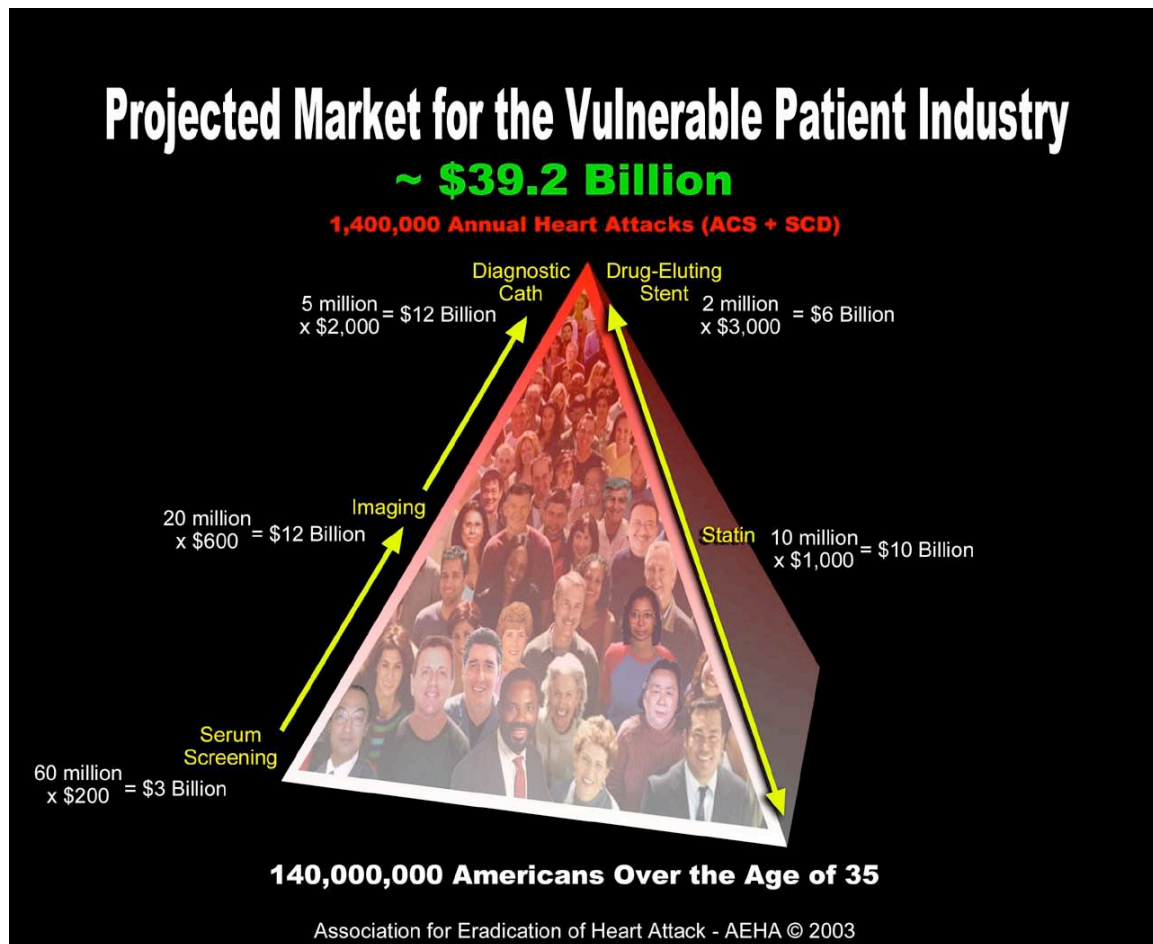
INTRODUCTION:

VULNERABLE PLAQUE is a term coined by Dr. James Muller and colleagues from Massachusetts General Hospital to describe the types of atherosclerotic plaques at risk for erosion, inflammation, swelling and rupture without warning, resulting in a sudden cardiac event (acute coronary syndromes and/or sudden cardiac death. These plaques share common pathological features: a thin, fibrous cap; lipid-rich core and macrophage-dense activity near its surface.

The term “*vulnerable patient*” was proposed in a consensus statement developed by leading cardiovascular investigators – (the effort was organized by [the Association for Eradication of Heart Attack-AEHA](#)) to identify individuals in high risk of developing sudden cardiac events in the near future. In this population, however, vulnerable plaque is not the only the major cause of cardiac attacks, but also from blood prone to thrombosis (vulnerable blood) and electrical instability of the myocardium (vulnerable myocardium) resulting in fatal arrhythmias.



Every year, approximately 1.4 million Americans and 20 million worldwide experience a sudden cardiac event, a majority of which is clinically silent until hours to minutes before the attack. According to a recent Fortune magazine article (June 2002), the market for diagnosing and treating vulnerable plaque could reach \$10 billion or more by the end of 2010.



DETECTION:

Major and minor criteria¹ are being proposed for the detection of vulnerable plaque. The existence of one or more of these characteristics may constitute higher risk of plaque complications.

Major Criteria:

1. *Active inflammation* is identified by massive macrophage accumulation.
2. *Thin cap with large lipid core* with a cap thickness of < 100µM and a lipid core amounting to > 40% of plaque's total volume.

3. *Endothelial denudation with superficial platelet aggregation*, characterized by superficial erosion and platelet aggregation or fibrin deposition.
4. *Fissured or injured plaque* are prone to occlusive thrombi or thromboemboli.
5. *Severe stenosis* of greater than 90%.

Minor Criteria:

1. *Superficial calcified nodules*.
2. *Glistening yellow color of plaque* that indicates a large lipid core and thin fibrous cap, suggesting a high risk of rupture.
3. *Intraplaque hemorrhage* that may suggest plaque instability.
4. *Endothelial dysfunction* which may predict CHD and stroke.
5. *Expansive (positive) remodeling* - considered a marker of plaque vulnerability.

Current diagnostic modalities to detect vulnerable plaques, including invasive and non-invasive techniques and serological markers are designed to identify the various pathological components. Recent advances in intravascular imaging have significantly improved the detection of vulnerable plaque, however, limitations still exist.

Coronary angiography, long considered the “gold standard” for diagnosing luminal narrowing does not provide accurate information within the vessel walls necessary for the detection of vulnerable plaque. This limitation has prompted industry in providing alternative invasive and catheter-based techniques to directly visualize the vessel walls and to characterize plaque composition.

DIAGNOSTIC MODALITIES:

Invasive techniques:

1. *Intravascular Ultrasound (IVUS)*
IVUS can visualize the extent and distribution of atherosclerotic plaque by using a miniature transducer at the end of a flexible catheter. It provides a 2-D cross-sectional image of the arterial wall and plaque morphology. Findings can either be described as *echoreflexive*, *hyperechoic*, and *hypoechoic*, corresponding to calcified plaque, fibrous plaque and lipid-rich core, respectively. Potential artifacts can arise from this technique. Limitations include issues of resolution and inability to accurately distinguish between fibrous and lipid-rich plaques.

2. *IVUS Elastography (palpography)*

Elastography/ Palpography is based on the principle that tissue components with particular histopathologic contents differ in hardness and are expected to be compressed differently if a definite pressure is applied. Thus, assessments between hard tissues (i.e., calcifications and collagen) and soft tissues (i.e., lipids) as well as the mechanical properties of the vessel wall can be determined. This technique combines ultrasound images with radiofrequency measurements to identify regions of increased radial strain (high circumferential stress) that are high risk to rupture. This feature improves on the limitation of differentiating between lipid-rich and fibrous plaques seen in standard IVUS.

Elastography also demonstrated a positive correlation between strain measurements and macrophage-dense activity and an inverse relation with the quality of vascular smooth muscle cells within the plaque. However, this technique is, at present, unable to discriminate between normal arteries and early to advanced fibrous plaques. There is also major difficulty in acquiring data in a pulsating artery located within contracting myocardium.

3. *Angioscopy*

This modality utilizes fiberoptics for direct visualization of coronary arteries. Angioscopy characterizes plaque composition and shows the existence of thrombus and endoluminal irregularities such as fissures, ulcerations, and tears. In this technique, normal arteries appear as glistening white, while atherosclerotic plaques can appear yellow pertaining to cholesterol-rich crystals seen through a thin, fibrous cap or white referring to the presence of a thick, fibrous cap. Yellow lesions most likely correspond to vulnerable plaque. The limitations of current system designs include the need to create a blood-free field, subjectivity of color interpretation, and the decreased sensitivity to detect subtle alterations in plaque composition.

4. *Optical Coherence Tomography (OCT)*

OCT measures the intensity of reflected infrared light, derived from a laser light source directed at the tissue. This modality has superior resolution over IVUS, allowing identification of plaque characteristics such as intimal inflammation, extent of macrophage infiltration, lipid-rich regions as well as internal and external laminae. The thickness of the fibrous cap overlying the atheroma can also be assessed. Limitations include poor penetration in large tissue volumes, interference from blood, relative slow data acquisition rate and multiple scattering.

5. *Thermography*

Inflammation that contributes significantly to the pathophysiology of vulnerable plaques creates local elevations in temperature that can be detected using specially designed thermography catheters of 3 French size. All catheters require direct contact with the vessel wall. Concerns relating to its effectiveness in assessing specific plaque vulnerability, possible vessel injury and dependence on use of high-resolution imaging modalities for structural definition have been identified as limitations.

6. *Spectroscopy*

Different energy sources are used for the detection of plaque, including infrared and laser. The technique shares with thermography the limitation of having to be dependent on an imaging modality such as IVUS, angiography or OCT to provide structural definition.

A) *Raman Spectroscopy (RS)*

A single wavelength of laser light is directed onto tissue samples to identify gross chemical changes in the tissue and can also effectively distinguish between lipid-rich, fibrous and calcified plaques. RS can examine tissue beneath fibrous caps and within the antheromatous core. Current limitations are the strong background fluorescence within the optical fibers of the catheter-based system, laser light absorption by blood, poor tissue penetration, and low signal-to-noise ratio.

B) *Near-infrared Spectroscopy (NIRS)*

Infrared light is used as an energy source that permits deeper tissue penetration to identify individual components of plaque.

Non-invasive techniques:

1. *Electron Beam Computed Tomography (EBCT)*

EBCT is a technique of imaging coronary artery calcium that uses a faster rate of imaging than conventional CT. An EBCT finding of calcium correlates with significant stenosis (> 50%) on coronary angiography. It may serve as a screening tool and can be particularly helpful in patients with an equivocal exercise test. However, plaques prone to rupture often lack calcium and the site and extent of calcification does not necessarily equate to site-specific stenosis.

2. *Magnetic Resonance Imaging (MRI)*

MRI is an excellent modality in visualizing fibrous cap thickness, plaque rupture, arterial thrombi in vivo, and in assessing effects of treatments such as lipid-lowering therapy. MRI currently lacks sufficient resolution for accurate measurements of cap thickness and characterization of the atherosclerotic lesion within the circulatory circulation. Improvements in MRI are presently sought by inserting intravascular coils in the vessels.

Emerging Technologies:

Several developments to improve vulnerable plaque detection include pharmacological interventions that target specific receptor activation, cell metabolism, or biologic pathways in inflammation and plaque processes; application of intravascular catheter-mounted detectors; metal nanoparticles serving as contrast agents; molecular probes that exhibit enzyme-specific fluorescence; nanocrystals emitting photonic energy that serve as cellular beacons; and the development of microelectromechanical systems (MEMS) in intravascular imaging.

SUMMARY

Vulnerable plaque has been elucidated as a major cause of sudden cardiac events. Though the current techniques in imaging and biologic measurements enumerated have successfully detected these potentially fatal plaques, limitations are prevalent and there is not one optimal modality. A greater understanding of the pathobiology and natural history of vulnerable plaque is eagerly sought.

The challenges seen in vulnerable plaque are fourfold:

1. All coronary vascular territories require interrogation, which is a challenge for the invasive modalities.
2. A single interrogation at a single point of time will not confer knowledge about vulnerable plaque forever, and the duration of its relevance is unclear.
3. Effective treatment of vulnerable plaque may already exist (i.e., statins) or not, but detection and effective treatment will need to be married in order to make this exercise worthwhile.
4. Absolute numbers of people with subclinical coronary artery disease in the US are staggering and will challenge any modality in terms of its application.

In efforts to facilitate prevention and screening of vulnerable patients, the Association for Eradication of Heart Attack (AEHA) has invited a selected group of leaders and experts in the field to join the SHAPE (**S**creening for **H**eart **A**ttack **P**revention and **E**ducation) Task Force and help guide the initiative. The participants are invited to take part in a focus group meeting for preparing a consensus statement as a guideline for cardiovascular screening.

More information about AEHA and the National SHAPE Program can be found at <http://www.aeha.org/shape/index.asp>

The preliminary draft of the SHAPE proposal will be prepared and distributed two weeks prior to the AHA 2004 meeting.

The guidelines will also be published as Part III of the **Vulnerable Patient Consensus Statement** following the [Part I](#) and [Part II](#), which were previously organized and published by AEHA (Circulation Journal, Oct. 2003).

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